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OSTEOSARCOMA

A review of 96 cases

by

ÅKE LINDBOM GUNNAR SÖDERBERG and HARLAN J SPJUT

The classification of osteosarcoma has tended in recent years to become more sharply defined with the recognition of such growths as chondrosarcoma primary fibrosarcoma of bone and juxtacortical osteosarcoma as separate clinical and pathologic entities The largest single group of osteosarcomas published to date is a series of 430 cases from the Mayo Clinic covering the period 1909—1955 (COVENTRY and DAHLIN 1957) The authors reported in this group a five year survival of 19 3 % This figure is higher than that of many others who have had experience with this neoplasm JAFFE (1958) and LICHTENSTEIN (1959) stated that a five year survival rate after surgical therapy of osteogenic sarcoma is rarely over 5 to 10 % The five year survival rate in a Norwegian material was 10 7 % (EIDE et coll) Certain malignant tumors have for many years in Sweden been referred to a few central tumor clinics and it has consequently been possible to collect a large group of bone tumor cases in a Bone Tumor Registry at Karolinska Sjukhuset Stockholm We have among the osteosarcomas 96 cases that have been followed for a minimum of 3 years and which are reviewed in this communication

From the Institute of Radiopathology (Director Prof Lars Santesson) and Roentgen diagnostic Department D (Director Docent Å Lindbom) Karolinska Sjukhuset Stockholm Sweden Submitted for publication 3 February 1961



Fig 1 Influence of irradiation on vascularity of osteosarcoma a) Venous phase of angiography before treatment Many irregular vessels in tumor area Veins draining tumor are well filled and dilated indicating arteriovenous shunts through tumor vessels b) Same phase of angiography after irradiation Diminished vascularity with narrower draining veins no obvious shunt

Material The major portion of our cases came from the three radiotherapy clinics in Stockholm, Gothenburg and Lund A few cases from various other hospitals are included The material does not contain all the osteosarcomas in Sweden, from that standpoint the material undoubtedly represents unintentional selection No cases were chosen because of specific factors whether favorable or unfavorable Tumors located in the skull, facial bones and mandible have been excluded Only cases that had a histologically confirmed diagnosis during or before 1956, have been included Every case was followed

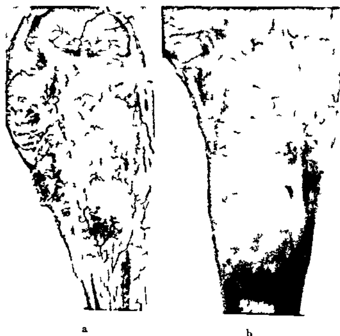


Fig 2 Influence of irradiation on tumor vessels Roentgenograms of d calcified section of injected specimens of two different chondroblastic osteosarcomas in p oximal end of tib a a) Highly vascular o teosarcoma not irradiated b) Another tumor after irradiation Only sparse vessels in tumor t ssue

Pathology Osteosarcoma is defined as a malignant tumor of bone with a sarcomatous stroma forming malignant osteoid and bone Areas may be fibrous or cartilaginous in fact these components may predominate Tumors of bone that are purely fibrous or cartilaginous without areas of osteoid or bone formation from the *malignant cells* are considered as separate entities and not as previously (CADE) included as osteosarcomas Juxtacortical osteosarcomas osteosarcomas arising in giant cell tumors and extra-osseous osteosarcomas have likewise been excluded from this series

In a number of our cases the tumor was examined by angiography prior to amputation the amputated specimen being injected with a fine barium suspension The vasculature was studied in the whole specimen and in de calcified thin slices of the tumor (LAGERGREN *et coll*) It was found that the growths were extremely vascular the anaplastic regions being more vascular than the better differentiated areas necrotic areas were poor in blood vessels or entirely devoid of demonstrable vessels In several cases decreased vascularity after irradiation was shown angiographically (Fig 1) Of special interest are two cases given preoperative irradiation therapy (one 7 000 r and the other



Fig 3 Osteoblastic osteosarcoma from distal end of femur of a 19 year old man Patient alive 20 years after amputation Hematoxylin eo in × 100

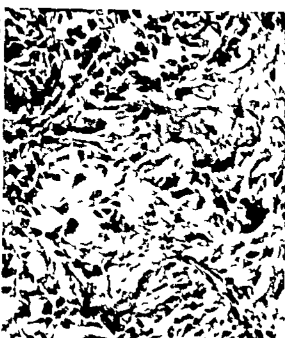


Fig 4 Photomicrograph of poorly differentiated osteoblastic osteosarcoma from humerus of 22 year old woman Patient alive 10 years after amputation Hematoxylin eo in × 240

3 000 r) The first of these cases does not belong to the series and is only mentioned for the purpose of illustration In the specimens of both these cases a great diminution of the vascularity of the tumor as compared to those that had not been irradiated was noted The tumor that received the highest dose presented histologic evidence of necrosis of the vessel walls with extravasation of blood The second sarcoma, of the chondroblastic type, had intact vessels with only focal necrosis of the walls (Fig 2) The decreased vascularity of the sarcomas after irradiation is probably due to necrosis and regressive changes in the tumor, perhaps supplemented by increased bone production or calcification in the malignant tissue

It is well known that the histologic pattern of osteosarcoma varies greatly We have classed our cases, as DAHLIN, into osteoblastic, fibroblastic and chondroblastic types depending on the dominant tissue element present In the cases subjected only to biopsy, or in which only one or two tissue sections were available, the classification was often difficult and arbitrary, two such cases were unclassifiable Commonly two of the elements were present, and in 17 specimens each of the three types was represented This classification was selected as a means of determining the influence on prognosis of the histologic type Differences in prognosis had been observed by DAHLIN

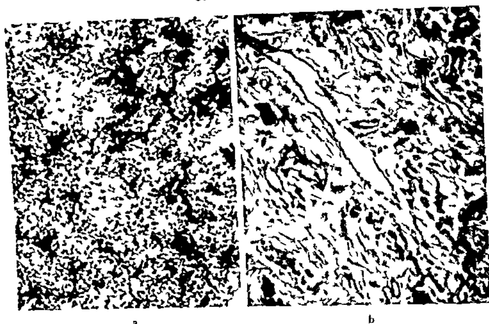


Fig 5 a) Biop y specimen of o teoblastic osteosarcoma from distal femoral metaphysis of 16-year-old boy Hematoxyl n-eo in × 100 b) Amputation after irradiation Extensive irradiation effect with a few large bi arre nuclei in the hyal nized stroma osteoid pattern still present Patient ali e 7 years later Hematoxylin eosin × 100

Of the 94 classifiable tumors 66 (68 7 %) were of the osteoblastic type 15 (15 6 %) of the chondroblastic and 13 (13 8 %) of the fibroblastic type A grading of the osteosarcomas into degrees of malignancy was not attempted An examination of the microscopic preparations left the impression that degree of differentiation bore little relationship to the survival of the patient histologically the neoplasms of the 5 year survivors were indistinguishable from those in which the patient died in a short time (Figs 3 4 and 5) PRICE (1952) reported a distinct correlation between the grade of malignancy of the osteogenic sarcoma and survival Most of the 5 year survivors were among those with tumors he classed as grade I but the work was based on 36 cases that included periosteal sarcomas and fibrosarcomas

Clinical features The situation of the tumors in the series was as follows in the femur in 39 cases tibia in 26 humerus in 13 pelvis in 5 ulna in 3, fibula in 3 bones of the feet in 2, ribs in 2 and in the sternum clavicle and scapula in 3 cases Fifty five (57 %) of the lesions were located in the region of the knee The age distribution is in accordance with other published series Fifty seven (60 %) of the patients were male and 39 (40 %) were female

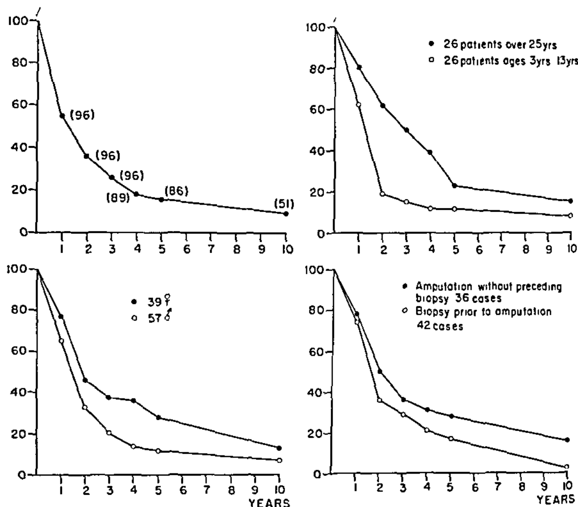


Fig 6 Survival curves a) Total material Figures within parentheses indicate number of cases at follow up b) Survival related to age c) related to sex and d) related to biopsy

Calculation of the survival rates has been made using both the time of histologic diagnosis and the onset of symptoms as the starting point (Fig 6) In a few cases the histologic diagnosis was not established for some time after the symptoms began, often these patients were treated by irradiation therapy first and later by amputation The differences of the survival rates when computed from the start of symptoms or from the time of histologic diagnosis were, however, insignificant Of the 86 cases eligible for 5 year survival 16 (18 5 %) lived more than 5 years from the time of diagnosis Of the 51 cases eligible for 10 year survival 9 (17 6 %) lived more than 10 years The 5 year survival covering all 96 cases was 16 6 % and will probably increase as there are three cases alive for more than 3 years and these have a fair chance of surviving The 5 year survival is thus not much different from that reported by DAHLIN Enquiries regarding 18 patients who lived more than 5 years

after the start of symptoms showed that 10 were still living Eight had died 4 of these died of the tumor and 3 of other causes In one case the cause of death was uncertain Nine patients have survived more than 10 years from the start of symptoms Six of these are alive 2 died from causes other than the sarcoma (autopsy) and in one the cause of death was unknown

We do not believe our material is large enough for a careful statistical analysis of subgroups of cases but we have divided the material into different factors that may be related to survival The age of the patients possibly had some effect on survival Twenty six of the cases were more than 25 years old and 26 cases were in the age group of 3 to 13 years The age group 14 to 24 years was excluded the two groups containing the oldest and the youngest patients were used for comparison The older group had a somewhat better survival rate than the younger (Fig 6) HAYLES et coll (1960) reported a 22 2 % five year survival for children with osteosarcoma the figures being essentially the same as those for the adults In our material the survival rate was slightly better for women than for men (Fig 6)

Preoperative irradiation had an unexpected effect in this material The survival rates of the preoperatively irradiated 50 cases and the 28 directly operated cases were identical at one two and three years but were better for the directly operated cases at four five and ten years We cannot fully explain this finding A few patients in the preoperatively treated group refused amputation and were then irradiated but had an amputation later when the tumor progressed further In these cases the delay in amputation increased the risk of spread of the tumor Possibly this was true also in those cases in which amputation was not delayed more than was necessary for the irradiation

Thirty six of the cases had amputation or resection done without prior biopsy There was a possible difference in the survival of the patients when compared to those who had had a preliminary biopsy (in most cases incisional) (Fig 6)

The chondroblastic and fibroblastic tumors possibly had a slightly better survival rate than the osteoblastic ones which is in accordance with DAHLIN s findings Females predominated in the group of patients with fibroblastic osteosarcoma (10 of 13) while there were more males among those with chondroblastic osteosarcoma (10 of 15), and in the osteoblastic osteosarcoma group (43 of 66)

No difference in survival could be detected between those patients having sarcomas situated distal to the knee and elbow joints as compared to those in which the tumor was located in the humeri or femori This is in contrast to the good survival rate observed by DAHLIN (1957) and HAYLES (1960) in osteosarcomas of the tibia There was no obvious difference between the survival of patients with small or large tumors The size of each tumor was measured in the earliest roentgenograms and ranged from 3 cm to 23 cm with 8 8 cm as the average diameter

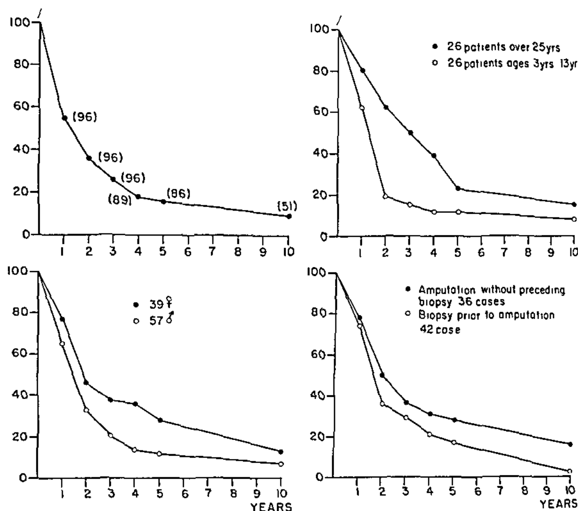


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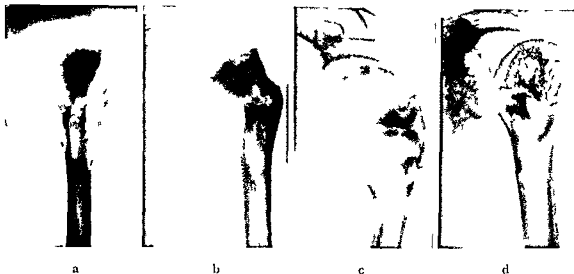


Fig 7 Chondroblastic osteosarcoma in boy aged 3 years and 9 months Irradiation following biopsy Patient alive after more than 10 years a) and b) Humerus before treatment a p and lateral c) Five months after irradiation Extensive calcification in tumor area d) Five years after treatment Slight deformity of the bone remains but no evidence of tumor



Fig 8 Same case as in fig 7 Biopsy specimen Poorly differentiated chondroblastic osteosarcoma Hematoxylin eosin × 100



Fig. 9. Chondroblastic osteosarcoma in a 10-year-old boy with extensive calcification after irradiation. a) Before. b) 3 months after treatment

Treatment

No standard method of therapy was used for our cases; treatment had greatly varied but was predominantly surgical. Seventy eight patients had either amputation or resection of the affected part; 18 had biopsy only and were treated with irradiation. Among these 18 patients were a number in which the location of the tumor made a surgical procedure difficult or impossible. Patients treated only with irradiation therapy had a poorer survival rate than those treated surgically. It should be noted, however, that the irradiation doses in these 18 cases were not high; the tumor dose rarely exceeded 3 000 r and was thus not of the order of 8 000 r recommended by CADE.

The effect of irradiation on the tumor was observed roentgenologically in several of the cases. Calcification and ossification in the tumor increased in many and in several could best be detected in the soft tissue component of the tumor (Fig. 7); in a few instances the tumor became surrounded by a shell of calcium (Fig. 9).

One of the cases treated by irradiation is unique. The patient was a boy



Fig 10 Osteoblastic osteosarcoma in 14 year old girl Typical roentgenographic appearance with sclerosis diffuse streaks of tumor bone in the extra osseous parts of tumor bone destruction and periosteal reaction Patient died of pulmonary metastases 3 months after onset of symptoms



Fig 11 Osteoblastic osteosarcoma from head of fibula of 31 year old man Well defined destruction and expansion of bone Atypical appearance The patient lived 15 years after local resection and died from bronchial carcinoma (autopsy)

aged 3 years and 9 months with a chondroblastic osteosarcoma of the upper end of the humerus After incisional biopsy, doses of 1 000 r to an anterior field and 1 000 r to a posterior field were given A great deal of calcification appeared in the tumor area The bone remodelled well and the patient became symptom free (Figs 7 and 8) The patient is alive without symptoms 12 years later and only slight deformity of the bone remains It is noteworthy that this patient was the youngest in our group and that the post irradiation sclerosis of the tumor was the most marked of the series

Two patients who had only local resection of the affected part survived more than ten years The tumor in one was located at the lower end of an ulna and in the other at the upper end of a fibula (Figs 11 and 19)

A comparison was made between five patients under 10 years of age and an equal number over 30 years of age who had received roentgen therapy and had follow up roentgenograms Reviewing the pre and post irradiation films of the two groups, one gained the impression that calcification was more marked in the younger age group

Roentgenographic findings

The initial roentgen films were available for study in all except 2 cases The following features were seen in the roentgenograms bone destruction in 72







Fig 12 Fig 13 a Fig 13 b

Fig 12 Osteoblastic osteosarcoma from femoral diaphysis of 44 year-old woman Well-delineated area of destruction with only slight periosteal reaction Atypical appearances Patient died from mitral stenosis after amputation No tumor found at autopsy

Fig 13 a) A p and b) lateral Another tumor histologically and radiographically similar to that in fig 12 from tibia of 18 year old man who died 6 months after amputation

cases bone sclerosis within the bone in 57, radiating or diffuse bone formation in the soft tissue component in 57 destruction of the cortex in 56 and periosteal bone formation in 59 cases

In 24 cases bone destruction sclerosis and new bone formation in the soft tissue component and periosteal bone formation were all present (Fig 10) These cases could be diagnosed as osteosarcoma on the basis of the routine roentgen examination

The films were studied to determine how many of the cases could be diagnosed roentgenographically as osteosarcoma Ninety two cases were used for this study and it was felt that 59 (64 %) could be classed as osteosarcomas As a generalization, it can be said that two-thirds of all osteosarcomas may be diagnosed with reasonable certainty from the roentgenograms alone Sixteen of the remaining cases presented ill defined areas of destruction of the bone Two of these had appearances suggestive of Ewing s sarcoma and

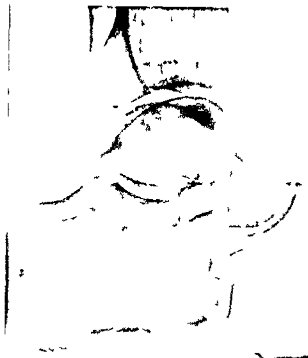


Fig 14 Osteosarcoma of benign appearance Well defined area of destruction in calcaneus of 27 year old man Amputation performed 2 years after curettage Specimen from latter considered benign Patient died 5 years after amputation from pulmonary metastases



Fig 15 Osteosarcoma simulating a fracture through a bone cyst in 6 year old boy Slight sclerosis in the metaphysis might suggest the true diagnosis

in one case the pelvic bone appeared to be the site of a metastasis Thirteen of the 16 cases merely presented roentgen features of a malignant tumor The roentgenographic appearances of 6 of the 92 cases were those of a benign tumor In 2 cases, they were typical of a giant cell tumor (Fig 11), and in 2 smooth walled cystic areas were evident in the femoral and tibial diaphysis (Figs 12 and 13), a tumor of the calcaneus was represented by a well defined area of destruction (Fig 14) The appearance in one case with a fracture of the upper end of the humerus was very much like a solitary bone cyst (Fig 15) and only after careful retrospective examination of the metaphysis and its comparison with the epiphysis could sclerosis be detected Two cases of acetabular osteo sarcomas were difficult to detect because of the small area of involvement, in fact in one case the tumor had been overlooked in the original films In the remaining 9 of the 92 cases the roentgenographic appearances varied widely and had no distinctive features, 4 of the cases were considered to be definitely malignant and in 4 others the possibility of a benign tumor was considered The remaining case, an osteosarcoma of a cervical rib, had no obvious roentgenographic changes In a few cases, the course and appearances suggested that the osteosarcoma had arisen in a pre existing lesion of unknown character (Fig 16)



F g 16 Fib obla tic osteosa coma f ll w ng sl wly p gres ing les n for 9 years in tibia of 31 year-ol l man Patient died of pulmon ary m tastases 4 m ths afte amputat on



F g 17 Ost osa coma in ferr u of 0 year old woman Atypical tumo wh ch s partly osteolytic and pa tly bone producing I at ent alive 16 years later

Of the 16 cases surviving five years 11 had typical changes (Figs 17 18 and 19) No differences were found between these 11 cases and the other typical osteosarcomas Five of the cases had appearances that were atypical Three of these were considered as malignant tumors and two as possibly benign As a group however the 16 did not differ much from those which



Fig 18 Osteoblastic osteosarcoma distally in femur of 9 year old girl Irradiation and 5 months later amputation as tumor had progressed It had just penetrated cortex Patient alive 11 years later



Fig 19 Osteoblastic osteosarcoma in 44 year old woman Tumor predominantly bone producing Patient alive 19 years after resection of ulna

did not survive 5 years The initial roentgen examination gives no indication as to the ultimate fate of the patient

Unusual cases One of our cases was similar to sclerosing osteogenic sarcomatosis reported by MOSELY and BASS (1956) The tumor was first detected in the proximal metaphysis of the left humerus of a 12 year old girl Marked new bone formation was present with similar changes in the same bone on the other side (Figs 20 and 21) The patient lived for 9 months after the tumor was diagnosed and died with lung and kidney metastases and involvement of several bones

A second case of multiple bone involvement by osteosarcoma also occurred in a 12 year old girl Two lesions, one in a femur and one in a humerus were examined by biopsy and diagnosed as fibroblastic osteosarcoma This patient lived two and a half years and died of lung metastases (Figs 22 and 23)

A woman, aged 41, had for ten years had a slowly growing tumor with gradually increasing pain and swelling in the region of the proximal part of the



a b

F g 20 Multipl foci of osteoblastic o teosarcoma in 12 year old g rl Au topsy 9 months after onset of symptoms showed wide spread metastases in skeleton and lungs a) Bone producing primary tumor fills the greater part of the medullary cavity and surrounds the shaft of the left humerus b) Several discrete lesions in r ght humerus

tibia The limb was amputated and the growth proved to be an osteogenic sarcoma The patient died two years later The roentgenographic appearances in this case were almost identical with those in another case with the same



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Fig. 18. Osteoblastic osteosarcoma distally in femur of 9 year old girl. Irradiation and 5 months later amputation as tumor had progressed. It had just penetrated cortex. Patient alive 11 years later.



Fig. 19. Osteoblastic osteosarcoma in 14 year old woman. Tumor predominantly bone producing. Patient alive 19 years after resection of ulna.

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Fig 27 Fibroblastic osteosarcoma with multiple skeletal foci in 12 year-old girl Patient died 2 5 years after onset of symptoms a) Osteolytic process in femur suggesting a giant cell tumor b) Lesion in a humerus

as carried out by CADE For these reasons our observations do not necessarily reflect the benefits or lack of value of irradiation therapy in osteosarcoma The youngest of our patients is alive more than 10 years after irradiation therapy only

Even though our figures indicate a possible increased risk of biopsy, we feel that the basic principle of preliminary biopsy of a tumor prior to surgical or irradiation therapy should be maintained Until a definitive diagnosis can be made without a biopsy or until proof of an added danger of biopsy is forthcoming the risk of the procedure should be accepted In the case of a tumor of bone biopsy carefully performed by a skilled operator carries a minimum risk of spread of cancer cells

Approximately two-thirds of all osteosarcomas present typical roentgenographic appearances A few may appear benign and some may simulate other malignant tumors e g Ewing s sarcoma and giant cell tumor of bone

SUMMARY

Ninety six cases of osteosarcoma are reviewed The majority of the tumors were situated in the region of the knee The five year survival rate was 18 5 Patients aged 25 or over



Fig 21 Same case as in fig 20 Representative section of the tumors an osteoblastic osteosarcoma Hematoxylin eosin × 40

localization in our bone tumor registry The latter case was, however, classified as a fibrosarcoma Both these cases were similar to the case published by HALL, BERSACK and VITOLO The long history suggests that it is possible that the tumor in these cases was secondary to an antecedent benign lesion of the tibia (Fig 16)

Conclusions

The prognosis in osteosarcoma has long been regarded as very poor When COVENTRY and DAHLIN published a five year survival rate of 19 3 %, this figure was generally considered as surprisingly high Our figure of 18 5 % however, supports these authors Although our material was not large enough for a careful statistical analysis, we have noted some trends The prognosis seems to be slightly better for women than for men and also slightly better in the older age group (above 25 years) than in the children Fibroblastic tumors were more common in women than in men, possibly this explains in part the better survival for women

Preoperative irradiation slightly decreased the survival rate Mention should be made that preoperative irradiation as given to the patients in this study varied greatly in quality and quantity There was no planned program such

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Fig 23 Same case as in fig 22 Tumor predominantly fibroblastic with foci of malignant osteoid Hematoxylin eosin × 100

had a better survival rate than the younger age groups The roentgen appearances of osteosarcomas are not always characteristic a few of the growths may appear to be benign and some may simulate other malignant tumors of bone The treatment is discussed

ZUSAMMENFASSUNG

Sechsundneunzig Fälle von Osteosarkom werden gesichtet Die Mehrzahl der Tumore war in der Kniegegend lokalisiert Die fünf Jahre Überlebensrate war 18 5 % Patienten über 25 Jahre haben eine bessere Überlebensrate als die jüngeren Altersgruppen Das Röntgenbild von Osteosarkomen ist nicht immer charakteristisch einige scheinen benign zu sein andere können anderen malignen Knochentumoren ähnlich sein Die Therapie wird besprochen

RÉSUMÉ

Les auteurs présentent quatre vingt seize cas d ostéosarcome La majorité de ces tumeurs siégeaient dans la région du genou Le taux de survie a cinq ans était de 18 5 % Les malades agés de 25 ans ou plus ont eu un taux de survie supérieur a celui des groupes d ages plus jeunes L aspect radiologique des ostéosarcomes n est pas toujours caractéristique un petit nombre de ces tumeurs ont un aspect bénin et d autres peuvent simuler d autres tumeur malignes osseuses Les auteurs étudient le traitement

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FROM THE ROENTGEN DEPARTMENT (DIRECTORS E DE FINE LICHT AND OLAF PETERSEN) AND DEPARTMENT OF OTOLOGY (DIRECTOR PROF N RISKÆR), COPENHAGEN COUNTY HOSPITAL, GENTOFTE, DENMARK

TOMOGRAPHY OF THE AUDITORY OSSICLES

by

S BRUNNER, OJVIND PETERSEN and P STOKSTED

The rise in the number of road accidents, with frequent traumatic injury to the skull, has considerably increased the incidence of fractures of the temporal bone The bone is usually fractured longitudinally, as FISCHER et coll found in 80 per cent of all their cases As mentioned e g by KETTEL (1957) in his description of an operation for the decompression of the facial nerve in cases of post traumatic facial palsy it is particularly this kind of fracture of the petrous part of the temporal bone which results in dislocation of the auditory ossicles It follows that cranial trauma is frequently followed by deafness or impaired hearing GROVE (1939) found ear symptoms with impairment of hearing in 32 2 per cent of 150 cases of cranial fractures

Another factor contributing to impaired hearing in the past was the inadequate surgical technique employed, which sometimes led to dislocation of the incus

The introduction of the operation microscope into otology radically altered the chances for performing tympanoplastic operations The absence of diagnostic aid sometimes forces the otologist to perform explorative tympanotomy as the conventional roentgen examination of the temporal bone, even with the Schuller, Stenver, Runstrom, Towne, and Chaussé projections, usually pro-

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Fig 1 Tympanic cavity seen from within with the ossicles in the normal anatomical position

vides information only of cholesteatoma pneumatisation and inflammatory changes but rarely reveal pathologic changes in or near the ossicles

The development of tomography has fundamentally altered the basis of radiologic diagnosis in otology By the use of suitable apparatus the tympanic cavity atticus and antrum the internal and external auditory meatus, the cochlea and semi circular canals the course of the facial canal and the ossicles may all be defined Pre operative tomography of the temporal bone has thus enabled otologists to plan a tympanoplastic operation and avoid exploration Tomography of the ossicles is of particular practical significance in congenital deformities cholesteatoma osteitic lesions and dislocations as a tympano plastic operation often makes it possible to establish an osseous chain of sound transmission

Anatomy A comprehensive knowledge of the anatomic relationships is a pre requisite for evaluating tomograms of the ossicles Fig 1 represents a bone dis section in which the topography of the ossicles in shown The handle and head of the malleus are located slightly in front of and more laterally than the long process and body of the incus Sound is transmitted via the malleus and incus to the stapes, the base of which rests on the oval window The handle of the malleus is connected with the tympanic membrane and the neck of the malleus is held in position by both the anterior and posterior ligaments the stapes is kept in place in the oval window by its annular ligament The incus, however, is retained by only a few strands of ligament including some from the body of the incus to the fossa for the incus, just as the incudostapedial joint is but loosely bound This is the weak point in the chain of the ossicles and dislocations of this joint as a result of trauma consequently lead to a displacement between the incus and the stapes



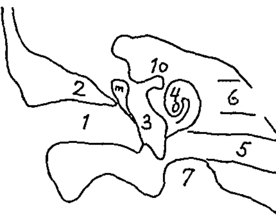


Fig 2 Frontal tomography Normal cut anteriorly through the tympanic cavity (3) external auditory meatus (1) spur (2) cochlea (4) pharyngo tympanic tube (5) internal auditory meatus (6) jugular fossa (7) facial canal (10) and malleus (m)



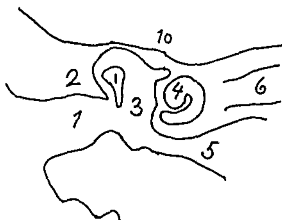


Fig 3 As in fig 2 but cut placed 2 to 3 mm more posteriorly Incus (i)





Fig 4 As in figs 2 and 3 but cut placed through semi circular canal (8) stapes (s)

Technique

Massiot s polytome has been found particularly suitable as a tomograph as its hypocycloid movement produces very good blurring of structures lying out side the plane desired furthermore, the polytome can produce quite thin cuts the thickness of the cut with the hypocycloid movement being 1 3 mm In describing the curve the tube traverses a distance of 4 5 m in 6 seconds and the greatest angle of deflection is 48

For demonstration of the ossicles we find it most suitable to perform tomography of the temporal bone with frontal and lateral sections

For frontal tomography the patient is placed in the supine position so that the median plane of the head and a line joining the external canthus of the eye and the tragus lie at right angles to the plane of the table The central beam is directed toward the glabella as the two sides are projected on the same film to facilitate comparison The anterior part of the tympanic cavity is visible on a cut at the level of the root of the tragus (Fig 2) Laterally the external auditory meatus (1) is seen to be bounded below by the tympanic part of the temporal bone and above by the so called spur (2) with the tympanic groove Medially the external auditory meatus is limited by the tympanic membrane which continues into the handle of the malleu The head of the malleus (m) juts like a club into the middle of the attic the intermediate ossicle the incus (i) being shown in cuts from one to a few millimetres posterior to this (Fig 3) The cochlea (4) appears in both this and the preceding tomo gram and the vestibule and semicircular canals (8) are outlined in cuts im mediately behind the cochlea (Fig 4) The stapes (s) lies in the same plane but is often difficult to demonstrate

For lateral tomography the patient is placed in the prone position with the head rotated so that a line through both external auditory canals lies at right angles to the table To make it easier for the patient to maintain this position, the shoulder on the side away from the table is lifted and the arm flexed while the other arm is extended parallel to the body Contrary to LANGFELT (1960) we prefer to let the ear under examination be the one further from the table, as the focusing is considerably easier the position less uncomfortable for the patient and the distances from the focus to plane of cut and from the plane of cut to film remain constant The central beam is directed towards the root of the tragus and by placing the plane of the cut between 2 and 2 5 cm medial to the lateral face of the mastoid process tomogram are obtained through the tympanic cavity Such a section is shown in Fig 5 in which the cut actually passes through the malleus (m) and the incus (i) It is seen that the body of the incus and the head of the malleus are ituated at the same level and further that the handle of the malleus and the long process of the incus are parallel to each other and lie in the tympanic cavity (3) Behind and above, a small part



Fig 5 Lateral tomography Normal cut through tympanic cavity (3) semi circular canal (8) facial canal (10) incus (i) and malleus (m) The long process of the incus and the handle of the malleus are parallel



Fig 6 Case 1 Frontal tomography showing displacement of incus (i) in relation to malleus (m)

of the semi circular canals (8) is evident and, behind and below, a small portion of the canal for the facial nerve appears (10) The mandibular joint can be seen lying anteriorly

As impaired hearing usually causes the patient great distress and often results in mental disturbances and difficulties in social adjustment, it is a matter of great importance to be able to diagnose the cause of the condition In the following cases of lesions of the ossicles, pre operative tomography made it possible to determine the changes, and thus plan the required operation for improvement of hearing

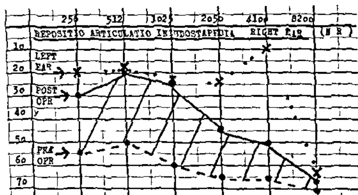


Fig 7 Case I Audiogram showing hearing in left ear (healthy side) and hearing before and after operation ——— in right ear

Case reports

Case I Boy aged 9 years Six years previously he had sustained a fracture through the right temporal bone (demonstrated in roentgenograms) No note of haemorrhage or discharge Hearing in the right ear had since been impaired Otologic examination disclosed that the patient could not hear a whisper at more than 0 10 m (normal 6 m) with the right ear Hearing on the left side normal The tympanic membrane of the right ear was intact but with residual scarring The ossicles were not seen clearly

Frontal tomography was performed Cuts through the anterior part of the tympanic cavity (Fig 6) revealed the presence of an ossicle like structure presumably the incus (1) lying laterally to the malleus (m) A dislocation must therefore have been present This was verified at operation as the chain of ossicles was broken with the long process of the incus displaced considerably backwards and rotated medially The incus was successfully reset and articulation with the stapes re established





Fig 8 Case 2 Lateral tomography showing displacement between incus (1) and malleus (m) and divergence between the long process of the incus and the handle of the malleus

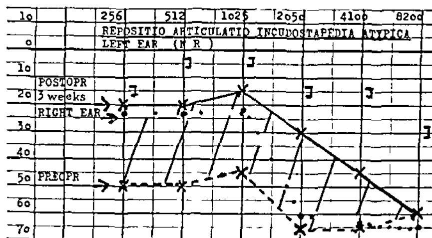


Fig 9 Case 2 Audiogram showing hearing in right ear before and after operation ———

The postoperative course was uneventful and the patient could hear a whisper with the right ear at a distance of 2 to 3 m Audiograms before and after operation are shown in Fig 7 The improvement in hearing is evident from the curves

Case 2 Boy age 13 years When six months old he had undergone bilateral simple mastoid ectomy Hearing had been considerably impaired since the operation and during the previous three or four years in spite of a hearing aid he had had difficulty in keeping up with his class at school Otologic examination established that a whisper could not be heard at more than 0 2 m there was scarring of both ear drums Left lateral tomography (Fig 8) showed that the body of the incus (i) was displaced downwards so that there was undoubtedly dislocation of the incudo stapedial joint It was not possible with certainty to differentiate the incus from the malleus however on the right side

On the strength of the roentgen findings operation was performed on the left side and the body of the incus was found to be considerably displaced with the long process of the incus



Fig 10 Case 3 Left lateral tomography showing displacement between incus (i) and malleus (m) and divergence between the long process of the incus and the handle of the malleus



Fig 11 Case 3 Right lateral tomography Only the malleus (m) is seen with certainty

pointing forwards Reposition of the incus was performed Recovery was uneventful and nearly normal hearing was obtained in the operated ear Audiograms before and after operation are shown in Fig 9 indicating clearly the improvement in hearing It is planned to re-examine the patient's right ear at a later date with a view to possible operation on that side

Case 3 Seaman age 23 years When two years old he had undergone resection of both mastoid processes recent impaired hearing had forced the patient to give up his occupation On physical examination the patient could not hear a whisper at a distance of more than 0 1 m the ear drums were dull in colour but intact Left lateral tomography (Fig 10) showed a downward displacement of the body of the incus (i) On the right side the incus was not visible with certainty whereas the malleus was clearly seen (Fig 11) At the subsequent operation it was found that the incus on the left side was dislocated with the long process directed inwards and forwards instead of downwards and inwards Reposition of the incus was per

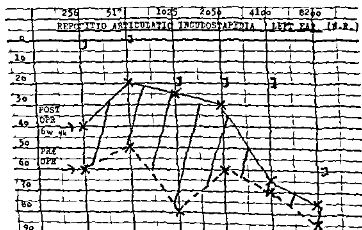


Fig 12 Case 3 Audiogram showing hearing of the left side before and after operation ———

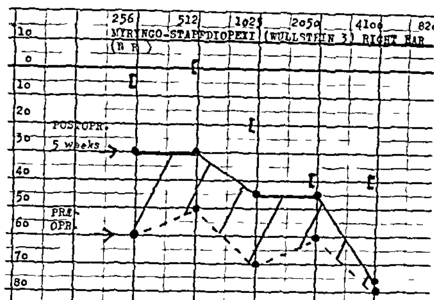


Fig 13 Case 3 Audiogram showing hearing on right side before and after operation ———

formed whereby normal articulation was re established Hearing was considerably improved as the patient was able to hear a whisper at a distance of 4 5 m on the left side as compared with 0 1 m previously as mentioned This improvement is apparent from the audiogram (Fig 12)

Operation on the right side was also performed but conditions here were less favourable as the roentgen examination had already suggested The incus was found to be totally dislocated forced downwards and wedged backwards It was thus necessary to displace the tympanic membrane onto the stapes But this also improved the hearing as the distance at which a whisper was heard increased from 0 1 m to 1 3 m The audiogram (Fig 13) shows the improvement in hearing on the right side

Discussion

The three case histories show that re establishment of the chain of ossicles led to considerable improvement in hearing, both in the patient with impaired hearing following trauma and in the patients with impaired hearing caused by earlier inadequate surgical technique, in spite of a lapse of 6, 12 and 21 years, respectively, between the primary trauma and the plastic operation Operation is facilitated by the fact that reposition need only consist in replacing the articular surfaces of the incudo stapedial joint, without consideration for scar formation or ankylosis, as the joint does not lose its capacity to transmit sound even though a considerable period of time has elapsed after dislocation Individual cases of successful operations for dislocation of the incus have been reported in recent years (Bauer 1958, Gisselsson 1958 and Elisberg & Floberg 1960) All these authors performed the operations on an indication of suspected

ossicle dislocation without being able to verify the diagnosis pre operatively as neither by ordinary otoscopy nor by use of Siegle s speculum were they able to confirm the condition

Conclusion

Tomography of the temporal bone should be carried out at the earliest opportunity in cases of impaired hearing following head injuries in order to eliminate possible dislocation of the ossicles

SUMMARY

Tomography enables dislocation of the auditory ossicles following a head injury or ear operation to be demonstrated The anatomy of the region is described and three typical cases are presented

ZUSAMMENFASSUNG

Mit der Tomographie kann eine Dislokation der Gehorknochelchen durch ein Schadel trauma oder eine Ohrenoperation demonstriert werden Die Anatomie wird beschrieben und 3 typische Falle werden vorgelegt

RÉSUMÉ

La tomographie permet de mettre en évidence la luxation des oss lets de l oreille apres un traumatisme cranien ou une opération sur l oreille Les auteurs décrivent l anatomie de cette région et présentent trois cas typiques

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FROM THE CENTRAL ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF KNUT LINDBLOM), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

VERTICAL CASSETTE STAND

by

PEKKA SOILA

The horizontally directed roentgen beam fulfills an important role in many roentgenologic examinations So may for example a search for fluid levels in the paranasal sinuses, the chest and the abdominal cavity be considerably aided by this technique Vertical cassette supports of different constructions which in some way can be attached to the side of the examination table are commercially available, they are often provided with a fluorescent screen However, cassettes are frequently supported only by sandbags and this often results in unstable and more or less oblique positioning of the cassette with consequent inaccuracy in the examination

A free standing vertical cassette stand of stainless steel is shown in Fig 1 This stand is easily manipulated and the cassette can rapidly be placed in the required position, as close as possible to the part to be examined It can be built for any standard cassette size A schematic drawing is shown in Fig 2, giving the measurements for cassette sizes of 24 × 30 cm and 35 × 35 cm

The problem of maintaining the balance of the cassette stand during an examination has been solved by means of attaching three rubber suction cups to its base They adhere to the surface of the examination table Any need for an extension of the stand towards the patient s side is hereby eliminated and the opposite side can be made short enough to leave sufficient room on any examination table for the different positions of the patient

Submitted for publication 14 December 1960



Fig 1 a) Vertical cassette stand b) Casette and grid mounted on the stand.

The groove of the cassette stand has been made sufficiently wide to accom modate a grid in front of the cassette a combination necessary in most ex aminations The clip which holds the upper end of the cassette in position is movable along the vertical limb of the stand to facilitate the use of cassettes of various sizes it also retains the grid We have found it advisable in practice however to have two sizes of supports available one for the cassette size 24 × 30 cm and another for the size 35 × 35 cm Provided that the suction cups function well the only difference between the two stands is the height of the vertical limb which is indicated by the letters (a) and (b) in Fig 2

In case fluoroscopy is required it may be carried out with the help of a port able screen whereafter the stand with the cassette can be placed in the desired position

Acknowledgement

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SUMMARY

A vertical casette stand of simple design is described

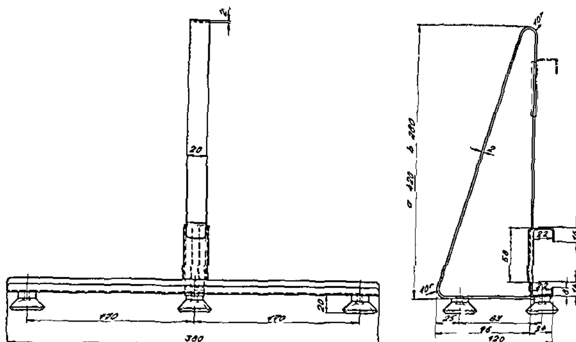


Fig 2 Schematic drawings showing the constructional details of the vertical stand for cassette sizes 24 × 30 cm and 35 × 35 cm The figures indicate the measures in millimeters

ZUSAMMENFASSUNG

Es wird ein einfacher vertikaler Kassettenhalter beschrieben

RÉSUMÉ

Description d'un support de cassette vertical de construction simple

FROM THE RADIUM CENTRE (DIRECTOR B JORGSHOLM), ODENSE, DENMARK

PALLIATIVE TREATMENT OF CARCINOMATOUS EFFUSIONS IN THE PLEURAL AND PERITONEAL CAVITIES WITH RADIOACTIVE GOLD

by

EILER LAMBRETHSEN and ARNE SELL

Cancerous conditions of the pleural and peritoneal cavities are often associated with considerable fluid formation Previously, the only palliative treatment was repeated tapping, possibly supplemented in the case of susceptible tumours with roentgen irradiation and hormone therapy although roentgen therapy to large abdominal or thoracic fields often gives rise to severe side effects which prevent the completion of a planned course of treatment

The introduction of treatment with radioactive isotopes (MULLER 1945 1950) marked a great advance as the method soon proved capable of affecting the fluid formation favourably without any marked side effects The substance preferred during the past 10 years has been radioactive gold Au^{198} Let it be emphasized at once that this form of therapy is also merely palliative

Physical and Technical data and Material

Physical data Au emits particle irradiation in the form of electrons as well as electromagnetic irradiation The mean range of the β irradiation in organic tissue is about 0 4 mm The γ ir radiation is more penetrating but makes up only a small proportion (about 15) of the total energy emitted by the disintegrating gold (BEIERWALTES 1957 LOW BEER 1950) Thus the main effect of the Au administered is obtained through the β radiation and only the superficial layers of the tumour-studded serous membranes are affected The half life is 2 7 days

Work carried out under a grant from the Danish Anti Cancer League Submitted for publication 16 September 1960

Fig 2 Schematic drawings showing the constructional details of the vertical stand for cassette sizes 24 × 30 cm and 35 × 35 cm The figures indicate the measures in millimeters

ZUSAMMENFASSUNG

Es wird ein einfacher vertikaler Kassettenhalter beschrieben

RÉSUMÉ

Description d'un support de cassette vertical de construction simple

Table 1

Distribution by site of primary tumour sex and age

Primary tumour	Number of cases			Mean age (years)
	Females	Males	Total	
Breast cancer	23	0	23	58
Ovarian cancer	21	0	21	51 6
Cancer of the lung	0	3	3	64
Cancer of the stomach	1	1	2	43
Cancer of the pleura	1	1	2	60
Cancer of the rectum	1	0	1	(66)
Sarcoma	0	1	1	(42)
Hodgkin s disease	1	0	1	(48)
Total	48	6	54	

risk of contamination as well as from a consideration of ease in training the personnel By the technique used, any manipulation of the vial holding the radioactive solution is avoided since it remains in the lead container in which it has been received After removal of the cover of the lead container two needles, a short afferent and a long efferent needle, are inserted through the rubber cap of the vial The short needle is connected, via a disposable infusion set with a bottle of sterile physiologic saline The pressure of the fluid in the saline bottle forces the gold solution through the long needle which is connected by rubber tubing with the needle inserted into the pleural or peritoneal cavity Immediately before the instillation we make sure that the needle is still in the serous cavity by ascertaining that there is a free flow of saline After the instillation the tubing and needles are discarded but are first kept in a safety compartment in a special container until the activity has subsided (5 or 6 half lives) Immediately after the instillation the patient is started on a fixed programme of frequent changes in posture in order to secure an even distribution of the radiogold We have not had an opportunity of 'scanning the patients with a view to checking the distribution of the isotope but in a few cases we have controlled the distribution by roentgen films

Present material The series comprises all patients treated with radioactive gold during the period July 1957 to November 1959, a total of 54 (Table 1) The majority were women the two groups of breast cancer and ovarian cancer being numerically the largest The average age may also be seen from Table 1 Out of the 54 cases 31 had pleural effusion 23 peritoneal carcinosis with effusion in 19 whereas the remaining 4 cases were treated prophylactically because of cancerous seedlings on the serosal surfaces A total of 84 instillations were administered

The series is heterogeneous and comprises cases of incurable cancer in a varying general condition

In analysing the material we included all the treated patients also those

The mechanism of the effect of the radioactive gold has been more or less established. It consists partly in an action upon the free cancer cells in the effusion (ANDREWS et coll. 1953) and partly in a lethal effect upon the superficial neoplastic lesions on the pleura or peritoneum. Furthermore, it is considered likely that radiation effects upon the serosal blood vessels and lymphatics may contribute to reduced fluid formation. The main portion of the instilled radioactive gold is phagocytized by macrophages and deposited in the serous membranes where it exerts its effect. A part of the gold particles is absorbed via the lymphatics and deposited mainly in the liver and bone marrow. Swedish animal experiments (FRITS et coll. 1959) indicate that the permeability of the serosa to Au^{198} may be altered by the administration of a high molecular polyphenol (polyphloretin phosphate) so that a smaller quantity of gold is absorbed and reaches the reticuloendothelial system. In addition the presence of neoplastic tissue on the serosa per se has proved to inhibit the permeability. Administration of such permeability inhibiting agents might be considered to be indicated mainly in prophylactic treatment with radioactive gold.

Technique. We used a colloidal solution of Au^{198}, instilled, after evacuation of the effusion, into the pleural or peritoneal cavity with a suitable quantity (200 to 300 ml) of normal saline. The pleural puncture is performed with an ordinary coarse needle, *left in situ until* the Au^{198} instillation which follows immediately. We use a trocar for evacuating the ascitic fluid, a few centimetres away from the trocar, an ordinary coarse needle is introduced through the abdominal wall into the peritoneal cavity and through this needle the solution of gold is instilled after removal of the trocar, the wound is closed with agraffes or sutures. This procedure was used in order not to risk leakage and contamination by the radioactive agent. The usual therapeutic dose of Au^{198} is 135 to 150 mC into the peritoneal and 75 to 100 mC into the pleural cavity.

Fig. 1. Installation set for Au^{198} therapy. Bottle with normal saline furnished with a disposable infusion set (a). Container of lead with vial containing colloidal suspension of Au^{198} (b).

The installation apparatus (Fig. 1) was simplified as far as possible in order to obtain the shortest possible installation period (radiation risk) and the minimum

Table 3

Effect of Au therapy (intrapleural instillation) assessed on the basis of the frequency of taps

Primary tumour	No of cases	Effect			Survival time in months				
		++	+	0	< 1	> 1	> 3	> 6	> 12
Breast cancer	18	9	1	8	5	13	10	8	5
Ovarian cancer	5	4	1	0	0	5	4	2	1
Cancer of the lung	3	1	0	2	2	1	1	0	0
Cancer of the pleura	2	1	0	1	0	2	1	1	0
Cancer of the rectum	1	1	0	0	0	1	1	1	0
Hodgkin s disease	1	0	1	0	0	1	0	0	0
Sarcoma	1	0	0	1	0	1	0	0	0
Total	31	16	3	12	7	24	17	12	6

operation had shown slight peritoneal seedlings of the cancer but no ascites Two of these patients have later died 72 and 80 days respectively after treatment and two are still alive without signs of ascites

Thirty-one cases of carcinomatous pleural effusions were assessed on the basis of the same criteria The results (Table 3) are in keeping with those of the intraperitoneal treatment, a little over half the cases (51 6 %) responding by a good palliative effect In this group there were 7 desolate cases the patients dying within one month of the treatment if these 7 cases are excluded a good palliative effect was obtained for about 75 % From Table 3 it will be noted also that 6 out of the 31 treated patients were alive one year after the first Au^{198} instillation i e about 20 %

As regards the average survival time after the first Au^{198} instillation this was 3 months 28 days in the intrapleural group of cases Nine patients are still alive 6 of them more than a year after the treatment Among the intraperitoneal cases the average survival time is 4 months 8 days Only two patients are alive more than one year after the first treatment The 4 patients having prophylactic treatment are not included

On the basis of the intervals between the taps and the quantity of tapped fluid we tried to calculate the daily fluid formation before and after the Au^{198} instillation in order to obtain yet another objective measure of the effect in addition to the frequency of taps (Fig 2) This could be done in all cases in the peritoneal group An unmistakable fall in daily fluid formation was observed in all those showing a good and moderately good effect of the treatment (assessed on the basis of the frequency of taps) In addition a fall in the daily fluid formation was found in 5 of the patients in whom the intervals between the taps were not lengthened In other words an effect of the gold therapy was found in 24 out of 34 intraperitoneal instillations, i e about 70 % In the case of the pleural effusions similar curves could not be traced in the same proportion of cases since the evacuation of the effusions could not always be complete

Table 2

Effect of Au¹⁹⁸ therapy (intraperitoneal instillation) assessed on the basis of the frequency of taps

Primary tumour	No of cases	Effect ++	Effect +	Effect 0	Survival time in months < 1	> 1	> 3	> 6	> 12
Ovarian cancer	12	7	1	4	4	8	6	3	1
Breast cancer	5	3	0	2	1	4	3	2	1
Cancer of the stomach	2	0	0	2	1	1	0	0	0
Total	19	10	1	8	6	13	9	5	2

who died within a month of the treatment and in whom it was difficult to assess the effect

Results

The object of the treatment was to reduce or possibly abolish the frequently considerable fluid formation associated with diffuse carcinosis of the pleural and peritoneal cavity, the patients would be spared repeated taps, and their general condition would be temporarily improved to an extent which would permit the institution of other palliative measures

It is difficult to assess the results and not easy to set up an objective measure of the effect We selected the frequency of taps before and after the instillation of Au^{198} as the most important criterion Like previous authors (SEAL et coll 1958) we have divided our series into 3 groups good, moderate, and no effect

I Good effect, ++ No tap during a period of at least 2 months This group, however, also includes patients who were tapped within a month of the Au^{198} instillation, if this last tap was followed by a period of at least 2 months without any tapping

II Moderate effect, + No tap during a period of a month or two after the instillation

III No effect, 0 Tapping needed within one month of the instillation This group also includes the patients who died within a month of the treatment

For the time being, we shall leave out of the intraperitoneal group four cases which had prophylactic instillations, since they cannot be assessed on the basis of the frequency of taps before and after instillation This leaves 19 patients (Table 2) treated by repeated taps before the instillation of Au^{198} A good effect was obtained in 10, or 53 %, ignoring 6 desolate cases dying within one month, there was a good palliative effect in 75 % Table 2 also includes the survival time after the first Au^{198} treatment, about 50 % of the patients survived for more than 3 months and about 25 % for more than 6 months Only 2 were alive one year after the first instillation

Four patients were treated with radiogold as a prophylactic measure against the development of ascites These were cases of ovarian carcinoma in which

cortical hormone) Concurrently with a total of 48 instillations leading to a good response 21 cases were receiving other forms of treatment in other words in almost half the cases supplementary treatment must be expected to have con tributed more or less to the favourable result although the curves show that the effect was due mainly to Au^{198} Diminution of major neoplastic lesions was not observed in any case after Au^{198} except in cases receiving supplementary roentgen therapy Reviewing the series in order to discover a possible haemostatic action of Au^{198} reflected by decreasing blood admixture to the effusion we found no such effect

Complications and Side effects

The complications and side effects were moderate and short lasting We grouped the side effects according to the time of their occurrence after the Au^{198} application No complications occurred at the time of the instillation, there was no record of accidental instillation into the abdominal or chest wall per foration of the bowel or pulmonary injury

During the first days after the instillation side effects were observed in about half the intraperitoneal cases in the form of one or more of the following symp toms pain or heaviness in the abdomen, nausea vomiting diarrhoea and elevation of temperature In the intrapleural cases the side effects were of a somewhat different nature increased dyspnoea cyanosis cough nausea vomit ing and elevation of temperature Well over half the patients complained of one or more of the named symptoms These side effects were not particularly severe and lasted only for a day or two

A group of secondary complications or sequelae appearing days or weeks after the instillations consisted partly of local changes and partly of more generalized effects including haematologic changes and exacerbation of the general condition in some cases fatal

A few authors (DENNIS et coll 1956 and ELKINS et coll 1956) have reported ileus as a complication to the intraperitoneal application of Au^{198} We observed this complication in four cases which are reported upon below

Case I Female aged 40 with inoperable ovarian carcinoma and marked ascites In the course of a 6-month period she received three Au instillations (130 150 and 150 mC) Two weeks after the last instillation she developed obstruction high up in the small intestine from which she died within two weeks Autopsy showed all the loops of the small intestine to be matted together by adhesions The peritoneal lining of the intestine was greatly thickened and of a dull pale blue colour There were also adhesions between the liver spleen and dia phragm No visible tumour tissue Histologic examination revealed thickening of the peritoneum and depositions of gold particles as well as diffuse carcinosis

Comment The patient died of adhesion ileus Autopsy did not reveal major tumour masses which might have induced th s condition Since the patient had not been subjected to surgery it must be considered likely that the adhesions were induced by Au these developed in the course of a period which could not have been longer than 5 months The third and last Au instillation possibly provoked the ileus

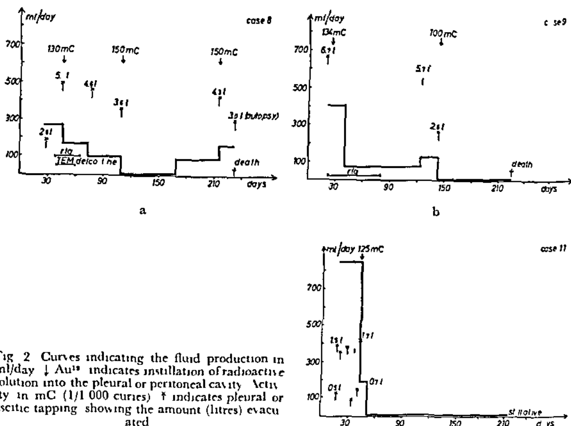


Fig. 2. Curves indicating the fluid production in ml/day. ↓ Au[198] indicates instillation of radioactive solution into the pleural or peritoneal cavity. Activity in mC (1/1 000 curies). † indicates pleural or ascitic tapping showing the amount (litres) evacuated.

Even so, we tried to evaluate the 18 instillations after which no effect was recorded or after which the patients died in a month: in 4 of these cases the daily fluid formation decreased.

Effect of repeated instillations. The 50 cases of effusion received a total of 80 instillations. A good effect of the first instillation was observed in 60 %. Nineteen patients had two instillations, with a good effect of the second instillation in about 50 %. Eight had 3 to 4 instillations, but only one of them showed a good effect from these last instillations. The intervals between the instillations varied considerably, from 2 or 3 weeks up to several months. The duration of the effect of an Au[198] instillation cannot be assessed accurately, but it may be estimated as being 2 to 4 months. In 3 or 4 cases we found that after the first less effective treatment, a long lasting decrease in fluid formation was obtained after the second instillation (Fig. 2a) when performed 4 to 6 weeks after the first. This indicates that the results may be improved by repeating the Au[198] application (possibly several times) at relatively brief intervals (2 or 3 weeks) (Hansen & Haug 1959, 1960).

A factor which must be considered in assessing the effect is concurrent treatment (roentgen irradiation, cytotoxics combined with adrenocortical hormone and, in cases of metastatic breast cancer, treatment with sex hormones or adreno-

the instillation but one week later she began to have frequent sanguineous slimy watery motions accompanied by rectal tenesmus Rectoscopy revealed haemorrhagic proctitis and a barium enema a spastic dehaustrated colon The patient was successfully treated with prednisolone and hydrocortisone enemas

Comment It seems reasonable to suppose that the Au^{198} was responsible for the syndrome suggesting ulcerative colitis Adhesions caused by the gynaecologic laparotomy may possibly have given rise to the formation of pockets around the descending colon so that the radioactive solution had no chance of becoming evenly distributed

Case 6 Female aged 70 with peritoneal carcinosis and ascites (primary tumour of the breast) Treated twice with intraperitoneal Au^{198} with a favourable effect After a third instillation about 6 months later she developed within two weeks non sanguineous diarrhoea which persisted for about a month Neither rectoscopy nor roentgen examination of the colon was performed. The patient died in a state of cachexia 3 months after the last instillation of Au^{198}

Comment Probable adhesions with pockets around the colon induced by the previous Au instillations

Among the intrapleural cases local secondary complications were extremely rare Pleural empyema occurred in two cases In one of these, the empyema was immediately associated with the instillation of Au^{198}, presumably because of lack of asepsis In the other case empyema was present at the time of the Au^{198} application the condition deteriorated and the patient died within a month The instillation of radioactive solution in this case was no doubt contraindicated

Haematologic changes Fifteen cases treated with radiogold exhibited decreased white cell and/or platelet counts in the peripheral blood In ten of them the changes may be ascribed to concurrent treatment (TEM combined with roentgen therapy) and the decrease was not more marked or more prolonged than in other cases treated with TEM and roentgen rays alone (JORGSHOLM 1959) Only 5 of the cases treated exclusively with Au^{198} showed moderate haematologic changes and these presented no problems

We wished to ascertain whether the Au^{198} therapy had in some cases aggravated the patients condition and possibly speeded the downhill course Out of the intraperitoneal cases a total of 10 died within one month of the instillation In 4 of them the treatment appeared to have aggravated the condition and precipitated the fatal outcome All these cases had large neoplastic masses in the abdomen and all four were in poor general health Out of the intrapleural cases 8 died within one month of the treatment All were in a poor general condition with severe cyanosis only moderately eased by pleural taps Several of them required permanent administration of oxygen In 5 of these debilitated patients we felt that the treatment had aggravated the condition but that we should not draw too far reaching conclusions

In order to find out why in some cases the treatment did not lead to the desired result we analysed the cases that failed to respond basing our assessment upon the frequency of taps In the intraperitoneal group 14 instillations were failures In 10 of these cases the general condition was poor at the time

Case 2 Female aged 50 with ovarian carcinoma and peritoneal dissemination Postoperative roentgen therapy to the abdomen followed later by triethylene melamine (TEM) and a little more than a year later Au^{198} (138 mC) intraperitoneally because of ascites and at the same time further roentgen therapy and TEM combined with prednisone A good effect upon the ascites was observed but at the end of 2 months it increased again and another instillation of Au^{198} (135 mC) was given Twenty four hours later the patient developed ileus and died immediately prior to the last instillation she had been feeling relatively well and had no abdominal symptoms Autopsy was not performed

Comment Unmistakable exacerbation occurred after Au^{198} with ileus provoked presumably by the instillation

Case 3 Male aged 55 with a history of gastric resection for ulcer in 1950 In January 1959 ileus preceded by several attacks of sub ileus Exploratory laparotomy revealed peritoneal carcinosis and ascites as well as numerous adhesions Immediately after the operation Au^{198} (100 mC) was administered intraperitoneally and 12 days later 150 mC One week after the last instillation the patient died apparently from an obstruction in the small intestine Autopsy showed the transverse colon stomach spleen pancreas liver and the anastomosed loops of the small intestine to be embedded in a great mass of tumour tissue and adhesions in addition there was diffuse peritoneal carcinosis

Comment The widespread adhesions were presumably due to the first operation The tumour tissue in the abdomen may explain the intestinal obstruction although the instillation of Au^{198} may have provoked it

Case 4 Female aged 47 with ovarian carcinoma and peritoneal carcinosis After a palliative operation she had roentgen irradiation to the abdomen TEM and Au^{198} (175 mC) intraperitoneally with a good effect upon the ascites The Au^{198} instillation was repeated 2 5 months later 150 mC being followed by repeated roentgen therapy and TEM Twenty days after the last instillation ileus developed (confirmed by roentgen examination) to which the *patient succumbed within 10 days Autopsy showed dissemination of cancer on the parietal* peritoneum a large neoplastic infiltration in the true pelvis and adhesions of the small intestine The bowel was of a dull pale blue colour and there was unmistakable thickening of the sub serous tissue There was no single obstruction but numerous stenosed areas were present in the small intestine due to the adhesions

Comment The patient died of an adhesion ileus The adhesions may have been due to the original operation but they may also have been caused by the Au^{198} The last instillation of Au^{198} may have provoked the ileus

All these four patients had received at least two instillations of Au^{198} A varying length of time after the latter instillation they developed ileus to which they succumbed The first two patients had no major tumour masses in the abdomen, whereas the latter two had neoplastic masses which may have caused the ileus Au^{198} may perhaps give rise to adhesions or may provoke ileus in cases with adhesions or major neoplastic masses, the spontaneous course of widespread abdominal carcinoma, with a marked tendency to ileus, must be borne in mind

Among other local secondary complications, we observed two cases of long lasting diarrhoea, as reported upon below

Case 5 A youngish woman who had been subjected to operation for ovarian carcinoma The operation revealed minute carcinomatous seedlings on a limited area of the peritoneum lining the true pelvis No ascites Three weeks later the patient had a prophylactic instillation of Au^{198} (150 mC) into the peritoneal cavity No complications occurred in connection with

Au^{198} instillations were given on an out patient basis (9 intraperitoneal and 6 intrapleural instillations), and in such an event the patient s next of kin must of course be informed of the situation and warned of the danger to children pregnant women and spouses of the fertile age

Autopsy on patients who die a short time after the instillation presents a special problem, due in part to the direct radiation risk to the autopsy staff and in part to the risk of contaminating utensils Manuals dealing with radia tion protection (BRAESTRUP 1958) recommend that autopsy, without special precautions, on bodies containing more than 5 mC radioactive isotope should not be performed in cases in which the activity is higher it is necessary to assess the time to be allowed for each postmortem in order not to exceed the permissible radiation dose

Discussion and conclusion

Our experience of radioactive gold therapy is in accordance with the reports of others (HANSEN et coll 1959 1960 DIAMOND 1958) i e a good palliative effect in about 50 % of cases of carcinomatous effusions in the peritoneal and pleural cavity It is worth stressing that this special procedure has gradually become an important link in palliative treatment, but let us not underestimate concurrent measures which have often contributed to the favourable result The main indication is rapid re accumulation of the effusion The dosage level was 135 to 150 mC Au^{198} into the peritoneal cavity and 75 to 100 mC into the pleural cavity Several examples showed that repeated instillation a few weeks after the first led to a surprisingly long symptom free period Supplementary measures were roentgen irradiation to localized major neoplastic lesions as well as hormone therapy and chemotherapy in suitable cases It is important to select patients in the best possible general health since the therapeutic results are considerably less favourable if the patients are in a poor general state In the latter cases we believe that gold therapy may contribute in aggravating the condition It is our experience moreover that in the presence of large widespread tumour masses no particular effect can be expected As far as the intraperitoneal cases are concerned there is also the risk of complications in the form of adhesions leading to ileus For this very reason, more reserve is now being displayed in using radioactive gold for intraperitoneal instillation and Thiotepa appears to be preferred as has been emphasized particularly by Swedish authors (KARLSTEDT) In cases of pleural carcinomatosis the same effect appears to be obtainable by the intrapleural administration of Thiotepa (MOLIN 1960) In patients with severe dyspnoea which persists after evacua tion of the effusion the effect of radiogold is very slight at times even un favourable In toto it may be stated that a poor general condition and large tumour masses particularly in the abdomen afford if not direct contra indications then at least every reason for a conservative approach

of the instillation, and in addition large neoplastic masses were palpable in the abdomen of 8. All 10 patients died within 39 days after the Au^{198} instillation. The remaining 4 were in a fairly good general condition without palpable tumour masses in the abdomen, they died of other causes within one month of the treatment (agranulocytosis, pulmonary atelectasis, pulmonary embolus, and ileus). It would therefore seem as if a poor general condition and large neoplastic masses in the abdomen hold out little hope of successful treatment, the expectation of life being short. Even in these cases, however, a few have responded by some decrease in the daily fluid formation. As far as the intrapleural cases are concerned, 18 instillations failed. Thirteen of these patients were in poor general condition, having severe dyspnoea and requiring in most cases permanent administration of oxygen. A number of the patients also had widespread neoplastic lesions in the lungs (primary cancer of the lung or metastases) or large cancerous seedlings on the pleura (4 cases). It must be assumed that a poor general condition and severe dyspnoea refractory to pleural puncture afford little prospects of effective Au^{198} instillation. Furthermore, cases with extensive pleural seedlings are not suited for this treatment.

The series includes two cases of pleural mesothelioma. One responded well to the instillation at the outset but two subsequent instillations were ineffective, at that time there was massive coating of the pleura with tumours. In the other case there was no effect upon the frequency of thoracocenteses but a moderate action upon the daily fluid formation. Others (Hansen et coll. 1959, Klingerman et coll. 1955) have reported favourable results of Au^{198} in pleural mesothelioma.

Protective measures. The precautions which must be observed in order to reduce the radiation risk to the staff as far as at all possible will be briefly considered. This problem arises in the following three situations: in the course of instillation, during the time immediately after the instillation, and in the event of autopsy.

It is important that the period of instillation and the manipulations with the radiogold should be as brief as possible. Furthermore, one must safeguard against leakage from the patient as already mentioned. It is often expedient to place the patient with the punctured side uppermost during the inflow and while the needle is being withdrawn. We did not carry out special measurements, but by a pocket dosemeter we ascertained that during an instillation procedure of 10 to 15 minutes, the whole body dose was about 10 to 15 mr.

While the patient is lying in the ward after the instillation, the protection problems concern almost exclusively the nursing staff. It must be enjoined upon the nurses to spend the briefest possible time in the vicinity of the patient and to stay as far from him as possible. In no case was the permitted weekly dose of 300 mr exceeded or even approached. It is advisable to keep the patient in hospital until the activity has decreased to about 30 mC. In several cases the

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SUMMARY

A series of 54 cases with carcinomatous effusions were treated by instillations of radioactive gold into the pleural or peritoneal cavity A good palliative effect was obtained in about 50 % Side effects and complications are reported and particular attention is drawn to the risk of adhesions leading to ileus The le favourable effect in cases in which the general condition is poor and in which large neoplastic masses are present in the pleural or peritoneal cavity is stressed

ZUSAMMENFASSUNG

Vierundfunfzig Falle mit karzinomatosen Ergussen wurden mit Instillation von Radiogold in die Brust oder Bauchhohle behandelt Ein guter palliativer Effekt wurde in etwa 50 % der Falle erzielt Nebenwirkungen und Komplikationen werden berichtet und besondere Auf merksamkeit wird auf das Risiko von Adhasionen gerichtet welche zu einem Ileuszustand fuhren konnen Der weniger gunstige Effekt in Fallen die einen schlechten Allgemeinzustand haben und bei denen grosse Tumormassen in der Pleura oder Peritonealhohle vorliegen wird hervorgehoben

RÉSUMÉ

Une série de 50 cas d épanchements cancéreux ont été traités par injections d or radio actif dans les cavités pleurale ou péritonéale On a obtenu un bon effet palliatif dans environ 50 % des cas Les auteurs décrivent les effects secondaires et les complications et attirent particulierement l attention sur le risque d adhérences provoquant une occlusion Ils insistent sur l effet moins favorable dans les cas ou l état général est mauvais et ou il existe de gro ses masses néoplasiques dans les cavités pleurale ou péritonéale

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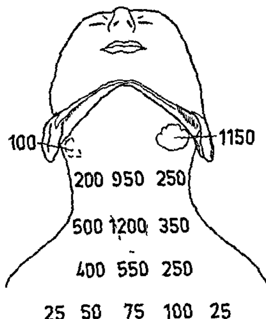
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The results of in vivo counting over the neck The numbers represent the net counts per minute obtained over the areas indicated Background of 150 counts per minute

About nine months later a hard lump the size of a hazelnut and not tender to palpation was found in the left upper cervical region and on withdrawal of the replacement therapy with triiodothyronine the patient rapidly became myxedematous Location studies with I^{131} indicated that the mass concentrated iodine (see figure) The total uptake in the neck was less than 2 per cent of the administered dose Conventional laboratory equipment was used for the examination a heavily shielded gamma scintillation detector (P 20C Tracerlab) with a 1 × 1 5 D thallium activated sodium iodide crystal in combination with a clinical scintillation collimator (P 25 Tracerlab) with the small angle insert (24 mm diameter bore) As there appeared to be evidence of a metastasis from the thyroid the left submandibular region was explored and the left submandibular salivary gland and surrounding tissues were removed en bloc microscopy revealed a normal salivary gland apart from some lymphocytic infiltration lymph nodes with slight inflammatory signs and a foreign body granuloma Analyses for radioactivity disclosed a much higher concentration of I^{131} in the salivary gland (0 0064 per cent of administered dose per gram of wet tissue) than in the lymph node (0 0009 % /g tissue) and the foreign body granuloma (0 0007 %/g tissue) Since the bulk of the operation specimen consisted of salivary gland it was obvious that the latter contained practically all of the radioactivity in the region

Discussion

The salivary glands in man possess the power to concentrate iodide (SCHIFF et coll 1947 et alii) The ratio between the concentration of I^{131} in the salivary

FROM THE DEPARTMENT OF MEDICINE (DIRECTOR JAN WALDENSTROM) AND THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR INGE GYNNING), MALMO GENERAL HOSPITAL, SWEDEN

SIGNIFICANCE OF UPTAKE OF RADIOACTIVE IODINE IN SALIVARY GLAND IN CARCINOMA OF THE THYROID

by

BENGT SKANSE, INGE GYNNING and INGE HEDENSKOG

Radioactive iodine is widely used in the examination of cases of malignant thyroid diseases and is particularly useful for locating functioning metastases We have recently observed that the uptake of radioactive iodine by a salivary gland may be misleading A search of the literature failed to disclose any reports of similar observations

Case report

A 29 year old woman who had had a lump in her neck for 10 years underwent thyroidectomy with left radical cervical dissection in 1957 the growth proved to be a follicular adenocarcinoma with lymph node metastases Preoperative studies had revealed that the uptake of radioactive iodine in the region of the tumour was lower than in the apparently uninvolved right lobe of the thyroid The lymph node metastases in the operation specimen were found to have taken up radioactive iodine the uptake per gram of wet tissue varying from 0 19 to 0 75 per cent of the dose of I^{131} administered Four months later a lump was felt in the right lobe of the thyroid and the patient was submitted to right total thyroidectomy with dissection of the cervical lymph nodes Microscopy revealed no signs of malignancy A part of the right submandibular salivary gland was removed at the operation as it appeared to be enlarged and was thought to be involved

A pea sized nodule appeared on the left side of the neck a year later it failed to concentrate iodine and was removed Microscopy proved the nodule to be a granuloma caused by a suture

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FROM THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR PROF J S MITCHELL), UNIVERSITY OF CAMBRIDGE ENGLAND

H^3 INCORPORATION INTO ASCITES TUMOUR AND TISSUE CULTURE CELLS EXPOSED TO SYNKAVIT AND ITS TRITIATED ANALOGUE

by

IRMELIN SIMON REUSS

In the clinical and laboratory studies of chemical radiosensitisers, which have been in progress in Cambridge since 1946 about 170 compounds have been examined (MITCHELL 1960a) The best chemical radiosensitiser is still the first compound selected for investigation This is tetrasodium 2 methyl 1 4 naphthaquinol diphosphate our Compound 1 (Synkavit Roche Products Ltd)

Further this compound is the carrier molecule for the radioactive drug which is being developed (HORWITZ et coll 1959, MITCHELL 1960b MARRIAN et coll 1961) For this purpose tetrasodium 2 methyl 1 4 naphthaquinol (6 T) diphosphate is being used This tritiated compound of high specific activity was first prepared by the method of reductive dehalogenation of tetra 6 iodo 2 methyl 1 4 naphthaquinol diphosphate (EVANS & MARRIAN, to be published)

The preparation used in the present investigation contains 13 curies of tritium per millimole all the tritium is firmly bound in the molecule It is to be noted that one atom of tritium per molecule corresponds to a specific activity of 29 1 curies per millimole so that the preparation studied here in these experiments contains 0 446 atoms of tritium per molecule It may be mentioned that preparations of still higher specific activity containing almost exactly 1 atom of tritium which is firmly bound per molecule are now readily

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glands and that in the serum varied between 4 6 and 11 2 in a case which had been given a large dose of radioactive iodine 59 hours before death (Cohen & Myant 1959) Stein et coll (1957) observed that the salivary I^{131} concentrations were highest in hypothyroid subjects and decreased as the thyroid activity increased *It is therefore hardly surprising that in our case* which had been subjected to total thyroidectomy a considerable part of the radioactive iodine in the neck region was found in the submandibular salivary gland Assuming that the submandibular gland had a normal weight of about 10g (it was not weighed), it contained about 0 06 per cent of the I^{131} administered Since the total activity in the whole neck was less than 2 per cent, the iodide concentrating capacity of the salivary gland must have been considerable The difference in iodine uptake between the left and the right submandibular region was most likely due to the removal of the right submandibular salivary gland at the second operation The iodide concentrating power of salivary glands may vary widely not only between different species but also in one and the same species (Cohen & Myant 1959)

A granuloma in the region of a normal submandibular salivary gland was mistaken for a functioning thyroid metastasis Such possibilities of error should be borne *in mind in the search for aberrant thyroid tissue and thyroid metas*tases with radioactive iodine techniques

SUMMARY

A case is reported which draws attention to the salivary glands as a source of error in the location of functioning thyroid metastases in the upper cervical region

ZUSAMMENFASSUNG

Die Verfasser berichten einen Fall welcher die Aufmerksamkeit auf die Speicheldrusen als eine Fehlerquelle bei der Lokalisation funktionierender Thyreoideametastasen in der oberen Halsregion richtet

RÉSUMÉ

Les auteurs présentent un cas qui attire l attention sur la source d erreur dans la localisation de métastases thyroidiennes sécrétantes dans la région cervicale supérieure que peuvent constituer les glandes salivaires

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Table 2

Ehrlich ascites tumour cells treated in vitro

Nos	Tritium	Activity mC/ml	Concentration of chemical compound	Time of treatment min	ARG exposure time hrs	Per cent of labelled cells	Autoradiographic grain counts per cell		
							Weak 10—60	Medium 80—200	Heavy 220—1 000
676—631	Tritiated compound I	60	5×10^{-4} M	2	48		Not countable too much background		
565—566		0 12	$1 \times 10^{-}$ M	30	72	All		+	
567—570					96	All			+
571—57				60	72	All			+
57 —576					96		Not countable too much background		
577—578				80	72	All			+
579—588					96		Not countable too much background		
639—650	Tritiated water	50		2	24—120	None			
6[illegible]3—6[illegible]4		1 0		5	24—120	None			
645—667	Tritiated water	50	+ cold Synkavit $5 \times 10^{-}$ M	2	24—120	None			
67[illegible]—68[illegible]		1 0	$1 \times 10^{-}$ M	30	24—120	None			

available from the Radiochemical Centre Amersham Buckinghamshire England (catalogue number TRA 72) Here it is relevant to mention that evidence of some degree of selective concentration of this compound in certain human tumours has been obtained in clinical investigations especially after intra arterial injection

The present investigation is a quantitative autoradiographic study to determine the time and degree of incorporation and the details of the distribution of the tritium of tritiated Compound I in certain adult embryonic and malignant cells In these experiments we have used tissue cultures of human amnion of the HeLa strain of human uterine cervical carcinoma and embryonic mouse fibroblasts together with the cells of the Ehrlich mouse ascites tumour (hyperdiploid strain of Lettre) both in vitro and in vivo The control experiments were made with comparable concentrations of tritium in the forms of tritiated water (T_2O) diluted in saline and of tritiated water diluted with solutions of non radioactive Compound I (cold Synkavit) In considering the details of the experiments it may be useful to refer to the summary of the results in Tables 1 2 and 3

Table 1

Tissue cultures treated with tritiated compound I, tritiated water and tritiated water + 'cold' synkavit

Nos	Material	Tritium	Activity mC/ml	Concentration of chemical compound	Time of treatment in min	ARG exposure time in hrs	Per cent of cell labelled	Autoradiographic grain counts per cell		
								Weak 10—60	Medium 80—200	Heavy 200—1000
620 583	E M F	Tritiated compound I	60	5×10^{-3} M	2	24	All			+
584					5	24	All			+
585					10	24	All			+
586					20	24	All			+
561			0 12	1×10^{-4} M	30	72	All	+		
562					60	72	All	+		
563					80	72	All		+	
564					120	72	All		+	
687	E M F	Tritiated water	50		2	24		Not countable too much background		
689			0 1		5	24		Not countable too much background		
721 A—723 B			0 1		15	72	13 0	+		
725 A—727 B			0 01		30	72	18 5	+ (mostly in dividing cells)		
688	L M F	Tritiated water	50	+ cold Synkavit $5 \times 10^{-}$ M	2	24		Not countable too much background		
690			0 1	1×10 M	5	24		Not countable too much background		
622	H A	Tritiated compound I	60	5×10 M	2	24	All			+
703—704			1 2	1×10^{-5} M	2	24	All		+	
695			0 12	1×10^{-5} M	30	72		Not countable too much background		
705—706	H A	Tritiated water	0 1		15	24	None			
707—708	H A	Tritiated water	0 1	+ cold Synkavit $1 \quad 10^{-}$ M	15	24	None			
621	HeLa	Tritiated compound I	60	5×10^{-3} M	2	24	All			+
624			0 12	$1 \times 10^{-}$ M	30	72	All			+ and more
699	HeLa	Tritiated water	50		2	5	None			
101			0 3		80	72	38 5		+	
701			0 1		5	5	None			
700	HeLa	Tritiated water	50	+ cold Synkavit 5×10^{-3} M	2	5	None			
702			0 1	1×10^{-3} M	5	5	None			



Fig 1 (No 565) Photomicrogram of ARG of Ehrlich ascites tumour cells treated in vitro for 30 min with tritiated Compound 1 (0 12 mC and 1×10^{-4} M ml) Magnification × 1 740



Fig 2 (No 713) Photomicrogram of ARG of Ehrlich ascites tumour cells treated in vivo for 30 min with tritiated Compound 1 Final concentration in ascites fluid 0 43 mC and 0 015 mg/ml Magnification × 1 740

Tissue culture techniques These experiments were carried out using three strains of cells embryonic mouse fibroblasts (E M F) the epithelium of human amnion (H A) and the HeLa human uterine cervical carcinoma The E M F and H A cells were used after two passages Stock cultures were maintained in the usual feeding bottles by the conventional monolayer technique The nutrient media consisted of (1) Eagle's medium in Hanks BSS 80 parts human serum 20 parts embryonic extract (chick) 10 parts for E M F and (2) Geys BSS 80 parts bovine serum 15 parts lactalbumen hydrolysate 5 parts for H A and HeLa

For the experimental cultures the cells were washed in saline free of calcium and magnesium removed from the bottles by scraping with a rubber policeman (a glass rod with a suitable shaped rubber-covered end) and dispersed by gentle pipetting After centrifugation the cells were resuspended in fresh medium and Petri dishes were inoculated with aliquots of the suspension Each Petri dish contained two (76 2 × 25 4 mm) microscope slides of 0 6 to 0 8 mm thickness These slides were previously coated with a sterile photographically inactive gelatine solution recommended for the stripping film technique in autoradiography (Boyd 1955)

It was found in the course of other experiments that even cells grown in a serum free nutrient fluid settled in monolayers on these slides and that the loss of cells through repeated washing was greatly reduced by their use. The details of the method are as follows dip grease free sterile microscope slides in a sterile solution composed of 5 g photographic gelatine 0 5 g chrome alum and 1 000 ml water The solution is sterilized by autoclaving at 5 lb (about 2 268 g) pressure

The Petri dishes were incubated in air containing CO_2 at 37 C for 24 hours The cultures were selected for the experiment when microscopic examination showed a well established monolayer of cells The slides were washed three times in warm Ringer's solution to remove serum and covered with the required dose of the appropriate radioactive solution for varying lengths of time at 37 C (see Table 1) After this treatment cultures were again washed in three changes of warm Ringer's solution fixed in 10 formalin in BSS for 30 minutes rinsed in tap water for 10 minutes then placed in distilled water and finally used for the autoradiographic studies

Table 3

Ehrlich ascites mice treated intraperitoneally in vivo

Nos	Tritium	Final concentration in ascites fluid		Time of treatment min	ARG exposure time hrs	Per cent of labelled cells	Autoradiographic grain counts per cell		
		Activity mC/ml	Concentration of chemical compound mg/ml				Weak 10—60	Medium 80—200	Heavy 220—1 000
633—638	Tritiated compound 1	20	0 65	5	48		Not countable too much background		
691—698		3	0 1	5	24	All	+		
709—711		0 43	0 015	20	6	All	+		
712—714					24	All	+		
740—743		0 24	0 008	20	24	All	+		
744—745					42	All	+		
752	Tritiated water	1 25		20	24	None			
753—754					48	None			
755					72	None			
756					96	14 5	< 5		
757					144	19 2	< 5		
715		0 022		20	5	None			
716—717					24	None			
718					48	None			
719					72	None			
720					144	None			
746		0 022		30	24	None			
747—748					48	None			
749—751					72	14 0	< 6		
758	Tritiated water	1 7	+ cold Synkavit 0 17	20	24	None			
759—760					48	None			
761					72	None			
762					96	7 8	< 5		
763					144	8 4	< 5		

Experimental methods

Radioactive preparations The specimens of tritiated Compound 1 batch No 20 (P/N No 012601) contained 13 curies per millimole The solution used contained 120 millicuries of tritium and 3 9 mg of the compound per millilitre

The control experiments were carried out with tritiated water of specific activity 1 curie per ml diluted with either Ringer s solution or/solutions of Compound 1 (cold Synkavit) in Ringer s solution to give specific activities of the final solutions comparable with those of the tritiated Compound 1



Fig 1 (No 56?) Photomicrogram of ARG of Ehrlich ascite tumour cells treated in vitro for 30 min with tritiated Compound I (0 12 mC and 1 × 10⁻ M/ml) Magnification × 1 740



Fig 2 (No 713) Photomicrogram of ARG of Ehrlich ascites tumour cells treated in vivo for 30 min with tritiated Compound I Final concentration in ascites fluid 0 43 mC and 0 015 mg/ml Magnification × 1 740

Tissue culture techniques These experiments were carried out using three strains of cells embryonic mouse fibroblasts (E M F) the epithelium of human amnion (H A) and the HeLa human uterine cervical carcinoma The E M F and H A cells were used after two passages Stock cultures were maintained in the usual feeding bottles by the conventional monolayer technique The nutrient media consisted of (1) Eagle s medium in Hanks BSS 80 parts human serum 20 parts embryonic extract (chick) 10 parts for E M F and (2) Geys BSS 80 parts bovine serum 15 parts lactalbumen hydrolysate 5 parts for H A and HeLa

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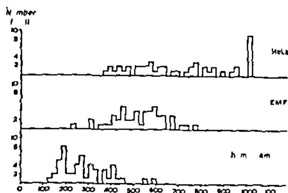


Fig 3 (Nos 620 621 622) Histograms of grain counts per cell in three tissue culture strains treated for 2 min with tritiated Compound 1 (60 mC and 5 × 10⁻⁸ M) Film exposure time 24 hours

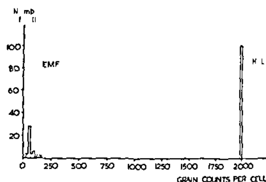


Fig 4 (Nos 623 624) Histogram of grain counts per cell of E M F and HeLa treated for 30 min with tritiated Compound 1 (120 μC and 1 × 10⁻⁴ M) Film exposure time 72 hours

Ehrlich ascites tumour cells The Ehrlich carcinoma (hyperdiploid strain of Lettré) is maintained by routine transplantation (0 2 ml every eighth day) into the peritoneal cavity of white mice of our laboratory strain of weight 28 to 35 g The experimental animals were used on the sixth day after inoculation

In vitro experiments Ascites fluid in an amount of 0 1 ml was added to 1 ml of the appropriate radioactive solution (see Table 2) All the procedures were carried out at 37 C The cell were spun down by centrifuging at 1 000 r p m for 2 minutes the supernatant radioactive solution was discarded and then six smears were made on gelatine coated slides The residue of cells was washed in 2 ml of warm Ringer s solution spun down again for 2 minutes and a further six smears made The smears were dried in air and autoradiographed

In vivo experiments The mice with Ehrlich ascites tumours were injected with 0 1 ml of tritiated Compound 1 tritiated water or tritiated water containing cold Synkavit intra peritoneally six days after inoculation The animals were killed at various time intervals the ascites fluid removed and its volume measured to determine the final radioactivity and concentration of compound in the ascites fluid (see Table 3) Smears were made by the method described above in the in vitro experiments

Autoradiographic technique Standard procedures were followed (Boyd 1955) Kodak AR 10 stripping film was used for making the autoradiograms (ARG) The exposure time for the films varied from 6 to 144 hours according to the amount of radioactive material present and was influenced by previous experience

The cultures and smears covered with the developed stripping film were stained with Ehrlich haematoxylin solution The percentage of labelled cells was determined by counting 500 cells in at least five different areas of each slide The results were analysed in the form of histograms of grain counts per cell

Results and Discussion

The quantitative results of all the experiments are summarized in Tables 1, 2 and 3 In the experiments using tritiated Compound 1 all the cells were

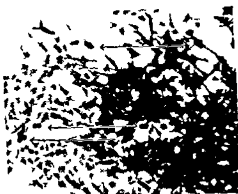


Fig 5 (No 674) Low power photomicrogram of ARG of HeLa culture in fig 4 Cells can be easily identified with their autoradiograms on the slipped film Magnification × 100



Fig 6 (No 693) Photomicrogram of ARG of corresponding E M F in fig 4 Magnification × 1 740

labelled after treatment both in vitro and in vivo The grain counts per cell increase with increasing specific activity and concentration of the solution and with increasing lengths of treatment The most surprising feature is the speed with which the tritium of the tritiated Compound 1 is incorporated into the cells Full labelling was observed in every cell of all the cell types used after two to five minutes treatment with tritiated Compound 1 (Fig 1) The same behaviour was observed in the in vivo experiments with the Ehrlich ascites tumour cells even at the lowest concentrations used (Fig 2) This rapid incorporation is consistent with the suggestion that the transport form of tritiated Compound 1 is the unchanged disphosphate (cf MITCHELL 1960a DRUCKREY and RAABE 1952) and that active transport into the cells is taking place

The control experiments (Tables 1 2 and 3) show that with solution of similar specific activities and concentrations, the passage of the tritium of tritiated water and of tritiated water in the presence of cold Synkavit depends on time Only after prolonged exposure a small percentage of cells were labelled in the tissue culture experiments There was no significant labelling of the Ehrlich ascites tumour cells either in vitro or in vivo The ordinary cold Synkavit thus had no effect No further studies of the rate of diffusion of tritiated water into the cells were required in these experiments

Histograms of the grain counts per cell were drawn out for each experiment Examples of them are given in Figs 3 and 4 The analysis of all the experiments shows that while all the cells are labelled the rate of uptake of tritiated Compound 1 is different in the three strains of cells in tissue culture The grain counts for 2 minutes exposure are shown in Fig 3

It might be thought that prolonged treatment would increase the relative

uptake in the normal cells That this is not the case can be seen in Fig 4, which summarizes the results for E M F and HeLa carcinoma cells treated with tritiated Compound 1 for 30 minutes Under these conditions the grain counts in these two types of cells differ by a factor of more than 100 Figs 5 and 6 are autoradiograms of cells from these experiments

These short term experiments demonstrate both qualitatively and quantitatively that there is selective uptake of tritiated Compound 1 into proliferating tumour cells

Acknowledgements

I am indebted to Mrs Thelma Prettejohn and Mrs Jeannette Davey for invaluable technical assistance and to Mr F W Mitchell for photomicrograms I am grateful to Professor J S Mitchell F R S for his interest and help

SUMMARY

Autoradiographic studies of living normal and malignant cells show a rapid incorporation *of the tritium of the tetrasodium 2 methyl 1 4 naphthaquinol (6 T) diphosphate into the* cells A selectivity of uptake by the tumour cells measured by grain counts could be demonstrated

ZUSAMMENFASSUNG

Autoradiographische Studien an lebenden normalen Zellen und an Tumorzellen zeigten dass obwohl alle Zellen schon nach einer kurzen Zeit mit dem Tritium von dem tetrasodium 2 methyl 1 4 naphthaquinol (6 T) diphosphate markiert waren konnte eine selective Speicherung in die Tumor zellen demonstriert werden

RÉSUMÉ

L auteur a étudié par histoautoradiographie l incorporation du tritium du tétrasodium 2 méthyl 1 4 naphthaquinol (6 T) diphosphate dans les cellules vivantes normales et cancéreuses Toutes les cellules sont marquées rapidement mais la numération des grains montre une fixation sélectives par les cellules tumorales

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FROM THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR B JOLLES) GENERAL HOSPITAL NORTHAMPTON AND THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR PROF J S MITCHELL) UNIVERSITY OF CAMBRIDGE, ENGLAND

INDIRECT RADIATION EFFECTS AND DIFFUSIBLE FACTORS IN IRRADIATED TISSUES (STROMATEX)

by

B JOLLES, M REMINGTON and I SIMON REUSS

The description of indirect radiation effects is rendered more difficult by the terminology in use The term indirect action of radiation has two entirely distinct meanings according to whether it is used by radiochemists or radio biologists and radiotherapists For the former the indirect action is that on molecules not directly ionized or excited but which are exchanged as a result of absorption of radiation energy which has excited or ionized solvent mole cules giving products that then act as energy carriers

By indirect radiation effect in radiotherapy we mean that the effect is one of second reference the radiation produces a direct effect upon some cellular tissue components the change in which produces another effect This effect is an indirect one and is not produced directly by the radiation Outstandingly the skin is an organ which shows these effects By custom the term has come to be restricted to the biologic effects produced in a tissue as a result of a radiation induced injury to the blood supply

A clarification and a radical modification of both terminology and detailed conceptual significance of terms become imperative on the radiobiologic level, lest the confusion grows deeper and prevents a better understanding of im portant biologic phenomena Indeed the centring of attention on results of radiation effects on blood vessels and the neglect of (1) effects on cells caused

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by stromal effects, (b) the effects on cells and stroma in the irradiated tissues by the neighbouring tissues, (3) the effects on distant tissues by the irradiated tissues and (4) the influence of the distant tissues on the directly irradiated tissues, have acted as a stumbling block in the evaluation of radiobiological and clinical events

The experimental findings that tumours irradiated in vivo and immediately transplanted may grow while tumours left in situ for a few days after irradiation with the same dose and then transplanted are absorbed, the protective effect in *partial body irradiation*, the roentgen ray sieve effect, and also numerous clinical observations of distant effects, could be quoted as *different* aspects of various indirect radiation effects (JOLLES 1953)

Great difficulties are encountered, however, when we try to focus our attention on *extracellular events and study the humoral effects, some of which* are demonstrable by present day laboratory methods

The interplay of normal and irradiation injured tissues is best exemplified by *the course of the radiation reaction of the skin treated through a sieve or* grid The protection afforded by the non irradiated areas of skin, allowing a higher dose to the exposed areas, probably depends upon the diffusion from the irradiated parts of active products and on the recovery processes making their way from the normal into the irradiated tissues These two are intricately connected and their study has to be undertaken under special experimental conditions The protective role of normal tissues was shown experimentally (JOLLES 1941) when it was found that the dose required to produce a given degree of skin reaction increases as the size of the field diminishes, thus the degree of effect depends on dose times area, and not on the dose alone When an area was broken up into two or more irradiated sectors, separated by protected areas of skin, the damage produced in each exposed sector was the same as would be produced if the whole area were given a much smaller dose On the other hand, the degree of reaction of two adjacent areas of skin at varying distances from each other, when compared with that of a single area of skin on a *symmetrical site exposed to exactly the same dose* (JOLLES *1949, 1950*), showed that the reaction increases with the decrease of the separation This led to the conception of indirect radiation effects attributable to diffusible products in irradiated tissues Thus, while there is an increase of the skin reaction over two adjacent small areas, a different set of circumstances arises in the case of a large field treated through a multiperforated lead shield in which a reduction in skin reaction is obtained on account of the protective role of skin areas not directly exposed

The diffusible substances in irradiated tissues and recovery factors making their way from the normal non irradiated parts have given rise to much interest and controversy Although the interdependence of organs and tissues in the animal body should be beyond dispute in the particular field of radiation reaction the ideas about events in tissues following irradiation appear to have

been narrowed on account of the confines of the visible skin reaction limited exactly to the directly exposed areas

These narrow limits have been widened when it was shown — by a series of experiments on grafting of normal rabbit s skin into an irradiated bed and irradiated skin into a normal bed — that radiation effects become visible outside the irradiated area when some of the recovery and repair processes making their way from the non irradiated parts are engaged or neutralized not only by the radiation injury induced products, but also by the surgical trauma and scarring processes (JOLLES & GREENING 1958)

In our previous papers experimental studies on the indirect radiation effects were reported and also the work of other authors reviewed The study of these factors has passed the phase of demonstration, and the actual collection of biologically effective factors and the study of effects on mitosis in tissue cultures have been undertaken These studies are described in the present paper

The different processes forming together the phenomenon of inflammation be it due to chemical or thermal stimuli or to ionizing radiations are deeply involved in the radiation reaction The separation of the injury and recovery processes is one of the problems of radiobiology which has to be studied before any progress is made in the clinical and experimental fields

Comments on methods Since an increased capillary permeability is *prominent* also in the radiation reaction it was thought advisable to follow *in the course of* the study the technique used by MILES and WILHELM (1955) in their investigations of the *intermediary* factors causing increased vascular permeability in inflammation These authors used a vital dye *(Pontamine Sky Blue)* injected *intravenously* prior to injury and the degree of blueing of the affected skin area served to demonstrate the degree of increased capillary permeability

This would in a certain measure give a clue as to the optimum time for collection of some *of these factors* By injecting a vital dye (Pontamine Sky Blue 60 mg/kg i e 1 2 *ml/kg* of a 5 % solution in 0 425 % saline) into the marginal ear vein of rabbits who e depilated flanks were exposed over small *areas to doses of* roentgen rays generated at 100 kV *(HVL 0 11* mm Cu) it was possible to determine the time of the maximum of a well defined blue flush over *the irradiated area* This appeared *in* preliminary experiments within 2 hours after irradiation and lasted up to 24 *hours*

Experiments were then carried out on 26 stock farm bred albino rabbits each serving as a test and control animal Areas 2 cm in diameter on the depilated flanks were exposed to a dose of roentgen rays and at varying intervals of time after the irradiation the vital dye was injected The time intervals tested were 1 2 3 4 6 7 9 15 16 18 20 21 and 23 days and the most intense blueing was consistently *noted at intervals of* 1 9 and 16 days after irradiation with an occasional but less *consistent* reaction at 4 days and 20 to 23 days (Tables 1 and 2)

Table 1

Diffusible substances in irradiated tissues in time course experiments

Experiment No	Dose in r	Days on which areas were irradiated (intervals between irradiation and injection of Pontamine Sky Blue)	Days on which reaction occurred (intervals between irradiation and the most intense blueing reaction)
21	1 200	1 4 9 16	1 4 16
22	1 200	do	1 9 16
23	1 200	do	1 9 16
24	1 200	do	1 16
25	1 200	do	Negative
26	1 200	do	1 4 16
7	2 000	1 3 6 9 15 20 23	1 9 20 23
8	2 000	do	9 15
11	2 000	1 3 7	1
12	2 000	do	1
15	2 000	1 2 4 18 21	Negative
16	2 000	do	Negative

Table 2

Summary of the results of time course experiments which are shown in detail in Table 1

Time interval in days	No of rabbits irradiated	No of rabbits with positive reaction	Percentage of positive reactions
1	12	8	66
4	8	2	25
9	8	4	50
16	6	5	83
20—24	6	2	33

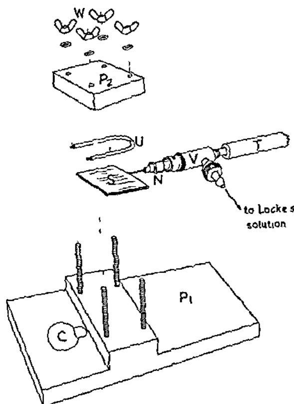
After having so established the optimum time for collection, it was decided to obtain samples from irradiated and control areas of skin of the same rabbit at 10 30 80 and 90 min, and 1 9 and 16 days after irradiation

Technique of 'stromatex' collection

In naming this factor, although its chemical nature is not yet ascertained, 'stromatex' was chosen because an extravascular, stromal origin is surmised (JOLLES 1960)

The technique of MILES and WILHELM (1958) was used here again The irradiated and control areas of skin are removed from the animal immediately after killing and are perfused with Locke s solution using the apparatus illustrated in the figure on opposite page

The skin (S) is placed, subcutaneous surface upwards, on the lower perspex



Schematic drawing of the perfusion apparatus

block (P_1) and a No 26 gauge needle (N) inserted into the skin below the dermis A rubber covered U piece (U) notched at the mid point to accommodate the thickness of the needle is placed on the skin covered by the second perspex block (P_2) and the whole clamped together tightly by means of wing nuts (W) A three way valve (V) is attached to the needle and a tuberculin type 1 ml syringe (T) and a reservoir of Locke s solution connected to the valve are used Locke s solution is drawn up into the syringe and injected under pressure of 3 to 4 atmospheres into the skin where it flows to the only free edge the direction of the flow being limited by the U piece The perfusate a fairly limpid opalescent fluid containing apart from Locke s solution and tissue fluids presumably some active substances in the case of irradiated skin collects in a well (C) in the lower perspex block below the free edge of the skin Forty international units of hyaluronidase are added to the first 0 5 ml of Locke s solution to facilitate perfusion

Table 3

Inhibition of mitosis by stromatex

	Experiment No.	Number of cells in mitosis as % of untreated controls: Prophase	Metaphase	Anaphase	Telephase	Total
Chick fibroblast cultures + perfusates from normal skin	A	98.9	102.5	91.5	97.5	99.0
	B_1	96.2	88.9	94.3	94.1	93.0
	B_2	96.2	88.9	94.3	94.1	93.0
	C	105.8	89.9	125.8	101.6	100.0
Fibroblast cultures + perfusates from skin irradiated 30 minutes previously	A	54.0	63.0	50.8	51.9	56.0
	B_1	45.3	48.7	41.4	38.3	43.9
	B_2	85.6	77.8	58.4	106.6	89.6
	C	60.5	49.5	91.5	48.5	53.3
	D	52.9	48.5	45.9	45.8	47.7

The perfusates from irradiated and non-irradiated areas of skin were subjected to various tests. One of these was upon mitosis in chick and mouse fibroblast and this was undertaken (I. S.-R.) at the Radiotherapeutic Centre in Cambridge.

Chick fibroblasts were cultured by the hanging drop method in plasma and embryonic extract, with or without perfusion fluid. The cultures were incubated for 24 hours, fixed and stained, and total mitosis counted in controls and in treated cultures. The perfusates obtained 24 hours and 16 days after irradiation showed no definite effect on mitosis. Perfusates obtained 10 min after irradiation produced some cytological abnormalities in mitoses, e.g. cell oedema, clumped chromosomes in metaphase and some sticky anaphase, but no mitotic inhibition. With perfusates obtained 30, 80 and 90 min after irradiation, however, a definite mitotic inhibition was observed and also nuclear abnormalities including accumulation of cells in meta- and anaphase, and clumped and fragmented chromosomes (Table 3).

Mouse fibroblasts were cultured on coverslips in Petri dishes by the monolayer technique and the perfusates incorporated into the supernatant nutrient fluid. Coverslips were removed at 24, 48 and 72 hours and mitosis counted on an average of a 1,000 resting cells. No effect on mitosis could be found with perfusates from skin irradiated 1.5 hours, 24 hours and 16 days previously. A slight effect on resting cells was seen at 24 hours, but by 72 hours all cells had recovered completely.

In a further series of experiments, perfusates have been injected into growing Crocker (S. 180) sarcoma in mice. The 30 min perfusate seems to have a slight inhibitory effect on growth, but so far the results are not numerous enough to form a definite opinion and the work is being continued (JOLLES and REMINGTON 1960).

Chemical studies, paper chromatography, electrophoresis and others, are being done. The lack of an inhibitory effect of the perfusates from tissues ir

radiated more than 90 min previously is not surprising when one assumes that the biologically active radiation injury products are either rapidly transported away from the site of their formation or are neutralized by the recovery factors of the surrounding non irradiated neighbourhood and by the intrinsic restorative power of the irradiated part of the skin not completely exhausted at these dose levels Observations made in grafting experiments showed that there was no marked difference between the fate of grafts kept in saline for 10 min and those kept for 60 min after irradiation This led to the belief that the diffusion of toxic substances took place over a period longer than one hour The more recent series of experiments shows that the activity increases from 10 to 30 min after which it decreases up to 90 min

Some of these experimental findings (e g the optimum time for the collection of the most intensely active perfusates and the length of time of their effectiveness) throw light on the time when recovery factors in irradiated tissues manifest themselves after radiation injury and explain the minimal effectiveness of diffusible substances on tumour not directly exposed to radiation

SUMMARY

The interplay of irradiated and normal tissues and the role of diffusible substances in the radiation induced inflammatory reaction are discussed The time at which the maximum yield of biologically active material is obtained from irradiated skin has been established in experiments with vital dyes injected into the animals at varying intervals after irradiation The technique of perfusion of rabbits skin is described and the results of tests on mitotic inhibition in tissue cultures of chick and mouse fibroblasts by perfusates from irradiated skin (stromatex) and normal skin of the same animals are given

ZUSAMMENFASSUNG

Die Wechselwirkung zwischen normalen und bestrahlten Geweben und die Rolle diffusibler Substanzen in der durch die Bestrahlung verursachten Entzundung werden besprochen Der Zeitpunkt an dem man ein maximales Sammeln biologisch wirksamen Materiales in bestrahlter Haut erhalt wurde in Tierexperimenten festgestellt in denen man Vitalfarben mit wechselnden Zeitabstanden nach der Bestrahlung injizierte Die Methode der Perfusion der Kaninchenhaut wird geschildert und die Ergebnisse der Untersuchungen uber die Inhibierung der Mitose in Gewebekulturen von Huhner und Mause Fibroblasten durch die Perfusionflussigkeit von bestrahltem Stromatex und normaler Haut werden beschrieben

RÉSUMÉ

Les auteurs étudient l influence réciproque entre les tissus irradiés et les tissus normaux, ainsi que le rôle des substances diffusibles dans la réaction inflammatoire due à l irradiation Le moment ou la peau irradiée fournit le plus de substance biologiquement active a été déterminé expérimentalement par des injections de colorants vitaux à des animaux à différents intervalles après l irradiation

La technique de perfusion de la peau de lapins est décrite les auteurs donnent les resultats d tests d inhibition mitotique sur des cultures de tissus de fibroblastes de poussin et de souris sous l effet de liquide de perfusion de peau irradiée stromatex et de peau normale de ces mêmes animaux

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FROM THE DEPARTMENT OF PAEDIATRICS, UNIVERSITY OF OTTAWA, CANADA

GENETIC HAZARDS OF RADIATION TO MAN
PART I

by

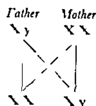
PAUL DE BELLEFEUILLE

Because greatly varying statements and inferences are forthcoming on the seriousness or the triviality of the genetic risks from radiation it is proposed here critically to review the available evidence In particular, it shall be indicated that a new analysis of the data gathered by the official U S Commission of enquiry in Hiroshima and Nagasaki compels one to question its generally negative conclusions An attempt shall be made to estimate the magnitude of the hazard which the present and the possible future levels of ionizing radiation pose to the posterity of man

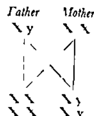
Experimental production of genetic effects

MULLER (1927) was the first to demonstrate the artificial transmutation of the gene on *Drosophila* by means of roentgen rays The production of hereditary effects by ionizing radiation has since been confirmed in a number of species the large amount of information on this question has been usefully reviewed by MULLER (1955) and W L RUSSELL (1954) Induced changes in the hereditary material may consist of major chromosome aberrations or breaks (giving rise to inversions deletions duplications and translocations) or to point or gene mutations (believed to represent molecular alterations within individual genes) All such induced changes are similar to the mutations which occur spontaneously and are due in part, it is thought to natural radio activity both external (ground cosmic rays) and internal (potassium 40 in tissues) The frequency of these changes may be increased by a variety of chemical mutagens and physical changes, as well as by ionizing radiations

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X an X chromosome bearing a (lethal) major aberration
The abnormal chromosome from the father can be transmitted only to a female conceptus which does not survive
(A recessive mutant gene would not be lethal in the heterozygous female embryo)



X an X chromosome bearing a (lethal) mutant gene
The mutant gene from the mother is lethal to a hemizygous male but if recessive does not affect a heterozygous female
(A dominant chromosomal change would be lethal for concepti of both sexes)

Fig 1 Sex ratio effects (sex linked lethals) According to the present genetic conception the proportion of males in the progeny may be increased by massive irradiation of the father s gonad and decreased by irradiation of the mother s

It is agreed that most, if not all, new mutations are deleterious In plants, much fewer than 1 % of radiation induced mutants are found to be useful In insects, a few induced mutations confer some advantage, but only to completely inbred populations — a situation quite in contrast with the human condition (NEWCOMBE 1960) According to DOBZHANSKY (1957) 'if anything, radiation induced mutants are more destructive than the spontaneous ones As far as genetic effects are concerned, *the only safe dose of high energy radiation is no radiation*

As observed in mammals, mostly the mouse, the effects of radiation induced mutations may be

(1) Dominant lethals, seen as reduced litter size or non lethals, evidenced as offspring which are malformed or diminished in vitality or life span, semi sterility, resulting from translocation, is seen one generation later as a reduction of litters by one half and is handed down to subsequent generations (PAULA HERTWIG 1940)

(2) Recessive mutations are demonstrated by mating the offspring of exposed males to females known to be (heterozygous) carriers of certain traits (W L RUSSELL 1954, CARTER et coll 1956)

(3) Mutations involving sex chromosomes may be reflected by a change in the sex ratio of the offspring (sex linked lethals, see Fig 1)

The production of mutations depends not only on the dosage of radiation (as reviewed in the next paragraph), but also on the kind of cells irradiated SCHINZ & SLOTOPOLSKY (1925) were the first to show, with testicular irradiation, that 'reserve spermatogonia are less sensitive than active spermatogonia Likewise, the sensitivity of oocytes, as measured by the induction of dominant lethals, is greatest when the interval between irradiation and mating is the shortest (L B RUSSELL & SPEAR 1955) However as will be seen presently, immature germ line cells are not immune to mutagenic influence Mutations occurring in mature gametes are demonstrable for a short time only, because after a period of *a few weeks (during which the subject* becomes temporarily

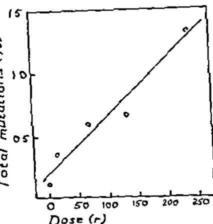


Fig 2 Dose-effect relationship in the production of mutations (dominant and recess e) in mice by chronic xposu e to roentgen rays As little as 13 r man festly accelerates the occurrence of mutations A least squares regression line has been drawn The regres on coefficient + 0 00448 per roent gen s h ghly s gnificantly d fferent from zero (t = 16 5ɔ p < 0 01) The l near correlation (r = 0 9ɔ5) is also significant (p < 0 0°) Based on data from CHARLES (19ɔ0)

sterile if the dose of radiation was massive enough) the injured gametes are replaced by new ones freshly matured from spermatogonia or oogonia For that reason a person accidentally exposed to a significant dose of radiation could by refraining from procreation for a few months, prevent the genetic effects most likely to be visible in offspring conceived early But that pre caution would not remove the probability that mutations induced in germ cells at an early gonial stage of development already observed by MULLER (1927) would be transmitted to many daughter cells eventually to many functional gametes and to the germ plasm of offspring These changes would be permanent as indeed they are in experimental animals where the magnitude of effect is found to be the same in offspring conceived early or late following the sterile period that is the mutation rate does not decrease with the time elapsed since exposure (W L RUSSELL) Such changes might or might not be evident in the first generation but could cause an increase of disease or disability in future generations In point of fact, as MULLER (1955) notes the less harmful a mutant the greater the number of individuals it affects inasmuch as reproduction remains possible Thus the total measure of mu tational harm is the number of mutations produced of whatever degree of harmfulness rather than the damage to any one individual or generation In a population which like the human is not inbred the generation showing the greatest effect of a mutation should be the first filial one, but the total effect in the posterity over an indefinite number of generations is still greater (CROW 19ɔ8) This point shall be illustrated in relation to the foreseeable effects of radiation upon descendants of man (see Part II)

Most classical work on the induction of mutations in mammals involved doses ranging from 200 to 1 600 r (HERTWIG, HENSON W L RUSSELL) What is most important in relation to human hazards is the significance of small amounts of radiant energy It is a clas ical finding in *Drosophila* and in lower life forms (bacteria bacteriophage) that the relation between dose and

effect is 'linear and cumulative, a given dose of radiation produces the same total effect, whether given at low intensity over a long period or in one large dose, and the linearity of the dose effect relation holds so constantly that no lower limit, or threshold, can be set for the mutagenic effect of roentgen rays (MULLER 1954) Indeed, MARCOVICH (1956), working with the lysogenic system of *E coli* K 12, sets a minimum effective dose below 1 r and postulates that a single photon of high energy radiation possesses mutagenic action

Although one frequently reads that the linearity of the dose effect relation has not been demonstrated in low dose irradiation of mammals, it is possible to show from CHARLES' (1950) experiments on the mouse a highly significant mutagenic action, with a significantly linear dose effect relation ranging from a minimum dose of 13 r (Fig 2) In one recent study, however, on sperma togonial mutations in mice (revealed by mating after the sterile period), pre liminary data indicate that chronic low intensity gamma radiation may produce a lower induced mutation rate per unit of radiation than acute subjection to high intensity roentgen rays (W L RUSSELL et coll 1958) This dose rate' effect, if confirmed by significant data, would modify the concept of a linear dose effect relationship, but need not invalidate the no threshold idea Rather, it could be explained by the presence in immature germ cells of something which affords protection or recovery from mutation at low intensity exposure, but is inhibited at high intensities of radiation It is also of interest to note in the same report that whereas chronic gamma irradiation of oocytes gave mutation rates lower than those from acute x irradiation of sperma togonia, acute irradiation of oocytes is at least as effective as acute irradiation of spermatogonia Thus women should be expected to be as vulnerable as men to the genetic hazards of massive irradiation

A number of writers have questioned the validity of extrapolating from the results of animal experimentation to man Indeed, one enthusiastic defender of so called stimulating' doses of roentgen rays to the ovaries for the correction of infertility (see Part II) has complained that 'too many doctors have been scared by fruit flies, mice, and men (ISRAEL 1952) However, one cannot discount the near certainty that the genetic effect of radiation, which has been proved in a number of species, is a general biological law to which man is no exception One could repeat here what RUGH (1958) says in re lation to foetal lesions every effect believed to be due to radiation in the human can be produced at will in the experimental animal Thus it seems that the only limitation to inferences from the animal to the human lies in the question of dosage In this connection it is of interest to note, with W L RUSSELL (1954), that dominant effects are induced by roentgen rays at a much higher rate in mice (with 20 haploid chromosomes) than in *Drosophila* (with 4) and that it is reasonable to suppose that, with 24 chromo somes in man, the rate in man might be somewhat higher than in the mouse' That the count of chromosomes in the haploid human cell is now known to be only 23 does not, of course, invalidate this thinking

Table 1

Studies of radiation mutagenesis in man. Mutation may be produced in man by doses of ionizing radiation in the higher diagnostic range

Sex	Effect	Worker	Kind of rays	Dose	Significance
♂	Congenital malformations in offspring of physicians with and without occupational exposure	MACHT & LAWRENCE 1955	Mostly roentgen chronic	25 r	p = 0 017 for all defects; p = 0 02 for heart dis
		CROW 1955	Same	Same	None
		TENTSHOV & coll. 1953	Same	Same	p = 0 07
♀ and ♂	Sex ratio changes in offspring of persons undergoing radio therapy	TURPIN, LEJEUNE & RETHORÉ 1956	Roentgen or radium therapy	Mean 721 r skin dose	p < 0 02 for mean dose 1 730 r
	Abortions in same	idem in U N Report p 195	Same	Same	p < 0 01
—	Chromosome aberrations in somatic cells in culture	BENDER 1957	Roentgen acute	25 r	p < 0 001

Estimated at 2.5 r/year (average gonad dose for radiologists see MRC Report 1956 *p 119) for a* period of 10 years between usual age of commencing clinical work (20 yrs) and mean age of fathers at conception of offspring (30 yrs)

See also Part II Table 5 (doubling dose 3.3 r)

Based on statistical analysis of author's data (comparison with controls)

It remains unfortunately true that the exact determination of the genetic hazard of radiation to man is fraught with many difficulties which have recently been reviewed by NEWCOMBE (1960) and are further analyzed below HALDANE (1958) sadly points out that the experimental work on mice which could give us most of the answers might have been done already for but a fraction of the cost of one H bomb The remainder of this study examines the direct evidence pertaining to the mutagenic effect of radiation in man

Clinical studies of genetic effects in man

Planned experiments similar to those just described have obviously not been possible with human beings Apart from the war time exposure of large populations to radiation which we shall study later one has to be content with surveys of human subjects who through occupational exposure or for therapeutic reasons have been subjected to ionizing radiation One such study conducted in the U S A by MACHT and LAWRENCE (1955) compared the incidence of twins foetal deaths and congenital defects in the offspring of two groups of physicians one (consisting mostly of radiologists) with occu

effect is 'linear' and cumulative, a given dose of radiation produces the same total effect, whether given at low intensity over a long period or in one large dose, and the *linearity of the dose effect relation holds* so constantly that no lower limit, or threshold, can be set for the mutagenic effect of roentgen rays (MULLER 1954) Indeed, MARCOVICH (1956), working with the lysogenic system of *E coli* K 12, sets a minimum effective dose below 1 r and postulates that a single photon of high energy radiation possesses mutagenic action

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♀	Congenital malformations in offspring of physicians with and without occupational exposure	MACHT & LAWRENCE 1955	Mostly roentgen chronic	[illegible]	$p = 0.01?$ for all defects; $p = 0.0?$ for heart dis.
		CROW 1955	Same	Same	None
		TENTSHOV & coll. 1959	Same	Same	$p = 0.0?$
♂ and ♀	Sex ratio changes in offspring of persons undergoing radiotherapy	TURPIN, LEJEUNE & RETHORÉ 1956	Roentgen or radium therapy	Mean 721 r skin dose	$p < 0.0?$ for mean dose 1,50? r
	Abortions in same	idem in U.N. Report p. 195	Same	Same	$p < 0.01$
—	Chromosome aberrations in somatic cells in culture	BENDER 1957	Roentgen acute	25 r	$p < 0.001$

Estimated as 2.5 r year (average gonad dose for radiologists, see MRC Report 1956, p. 119) for a period of 10 years between usual age of commencing clinical work (20 yrs) and mean age of fathers at conception of offspring (30 yrs).
See also Part II, Table 5 (doubling dose 33 r).
Based on statistical analysis of author's data (comparison with control).

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Planned experiments similar to those just described have obviously not been possible with human beings. Apart from the war time exposure of large populations to radiation which we shall study later, one has to be content with surveys of human subjects who, through occupational exposure or for therapeutic reasons, have been subjected to ionizing radiation. One such study conducted in the U.S.A. by MACHT and LAWRENCE (1955) compared the incidence of twins, foetal deaths and congenital defects in the offspring of two groups of physicians, one (consisting mostly of radiologists) with occu

pational exposure to roentgen rays, the other without such exposure The total number of offspring surveyed was 9 945 The significant differences found, which have been summarized in Table 1, were a higher incidence of congenital defects in the exposed group and a significantly higher ratio of males to females in the malformed offspring Among the defects, the categories showing the greatest differences were that of congenital heart and great vessel anomalies and, surprisingly, that of haemolytic disease of the newborn 'Neoplasms', including naevi and cysts, were more frequent, but not significantly, in the exposed group The differences retained their significance when an adjustment was introduced for the slight difference in mean parity (birth order) between groups However, doubts have been expressed (ABCC Report 1956, and U N Report 1958) on the reliability of this survey, which was conducted through mail questionnaires with unequal response in the two groups A similar study, reported by CROW (1955), bore on a comparison of about one quarter as many offspring of radiologists and of pathologists, and failed to show any difference in the numbers of foetal and neo natal deaths, sex ratio and malformations were not considered A recent report from Bulgaria (cf Table 1) gives results similar to those of MACHT and LAWRENCE

In France, TURPIN, LEJEUNE & RETHORE (1956) have studied the indicators of genetic change in 614 offspring of persons having undergone radio therapy involving the pelvic area The first data published were those on sex ratio According to hypothesis (Fig 1), induced sex linked mutations tend to increase the masculinity of the offspring of exposed men (or, at least, of those exposed heavily see p 75) and to reduce the masculinity of the offspring of exposed women Such an effect has been shown (Table 1) a significant difference exists in the sex ratio of the offspring of treated mothers and that of fathers having received more than 1 000 r (skin dose), whereas the offspring of the same parents, born before exposure, had not differed significantly in sex ratio The data on abortions, stillbirths and congenital malformations are available only in sketchy form (see U N Report 1958 p 195), in all 3 categories, there is a higher rate of wastage in the progeny of a parent exposed before conception than in that born to the same parent prior to therapy The difference for the abortion rate only is highly significant, in relation to both paternal and maternal exposure It is too marked to be explained by the obviously higher parity in post therapy offspring than in the pre therapy group

Relevant to the possible ill effects of small amounts of radiation on human populations is an epidemiological survey conducted in the state of New York (GENTRY et coll 1959) where the incidence of congenital malformation was found to be significantly higher in certain townships with high levels of natural radiation from the ground (granite outcrops, silicon rich rocks) than in other locations with low natural radiation Although the possibility is not excluded of other factors varying between mountainous regions and plains (standard

of living and nutrition oxygen tension available to the foetus) it seems reasonable to accept that the difference in incidence of malformation is causally related to the intensity of background radiation Another study to elucidate this point has been initiated on the population inhabiting the thorium rich monazite sands of Kerala India (Effect of radiation on human heredity 1957) no results are available as yet WESLEY (1960) has shown that the death certificate incidence of congenital malformation in many countries varies significantly with the geomagnetic latitude, to which is related the cosmic ray energy flux It must be noted however, that there is not a good agreement between available determinations of total background radiation in certain parts of the earth s surface and the intensity of cosmic rays, on the other hand there exist from country to country too great differences in living conditions degree of medical information, prevalence of autopsy and local concepts of what constitutes malformation (even when the W H O classification is observed) for this relationship to be convincing In any case, should the teratogenic effect of background radiation be documented more firmly one would not be certain whether it were mediated through the genes only or involved as well an influence on the embryo after conception

Atomic bomb studies of genetic effects in man

The most massive exposure of human persons to ionizing radiations took place in August 1945 in the Japanese cities of Hiroshima and Nagasaki The desirability of detecting any genetic effects of such exposure was recognised by the U S A sponsored Atomic Bomb Casualty Commission (ABCC Report 1956) To this end between February 1948 and February 1954 about 65 000 births in both cities were studied, the results were reported in great detail by NEEL SCHULL and many others In this publication referred to henceforth as the ABCC Report possible genetic effects are studied in relation to maternal age parity, maternal state of health parents socio-economic status as well as to exposure of the parents to the bomb For the latter factor the births (after eliminations of multiple births and of those from consanguineous unions) are distributed in a number of exposure cells according to a system of grades as follows for each parent

Exposure category	Defined as	Estimated dose (rep)
1	Absent from either city at time of explosion	0
2	Exposed lightly (more than 3 000 metres from hypocentre or nearer but with heavy shielding)	5 to 10
3 4	Exposed moderately (various combinations of distance and shielding)	50 to 150
5	Exposed heavily (within 3 000 metres and with major radiation sickness symptoms epilation, petechiae gingivitis)	200 to 500

Among the various factors which may influence the incidence of reproductive accidents, the maternal state of health and the parents socio economic status did not differ in these categories The relationship between exposure and maternal age, as well as parity, is discussed below

The general conclusion of the ABCC Report is that no consistent genetic effects of radiation could be shown in a study of the sex ratio and of the *incidence of malformations at birth, stillbirths and neo natal deaths* The authors add that only slight effects could have been detected in any case, and that their conclusions should not be interpreted as meaning that induced genetic factors were not, in fact, operating in the population The first point is important the near impossibility of showing marked effects in an unplanned experiment such as the nuclear bombing of even a large population has been stressed by PENROSE (1956) The large number of concomitantly varying factors, and the occurrence of reproductive accidents due to causes other *than radiation, must needs obscure the small portion of the total induced* genetic damage which could be detected in a partial survey of the first filial generation

It is felt, however, that the methods of analysis employed in the ABCC Report are open to a certain amount of review Of their rather complicated system of correcting the distance from the hypocentre by the amount of shielding (light, moderate or heavy) which may have protected the exposed person, the authors of the report themselves admit (p 44) that it is con *servative and has the effect of relegating to class 2 (exposed lightly) many* individuals who must have suffered appreciable radiation effects In a pre liminary publication, NEEL and SCHULL (1953) had indicated a significant effect of maternal exposure (without shielding correction) on the sex ratio, in 1956 they state that with the 'improved system of exposure categories, this effect is no longer significant A correction for shielding has not seemed necessary in other studies in which the incidence of microcephaly following prenatal exposure (MILLER et coll 1956), and that of leukaemia in all survivors *(YAMAWAKI 1953 MOLONEY & KASTENBAUM 1955)* both correlate well with the distance from the hypocentre, one may thus well ask if the shielding correction constitutes an improvement for any reason other than that it affords a more reassuring view *of the long term effects of atomic bombing* Be that as it may, this correction cannot be removed from the analysis of the data as presented in the ABCC Report and we must accept a certain amount of dilution of the lightly exposed group

In almost all of their analyses, the authors of the ABCC Report measure the statistical weight of the exposure of one parent, without taking into account whether the other parent was exposed or not thus in comparing the groups of births from unexposed mothers with those from exposed mothers, in each group the *fathers had been exposed to various degrees* in some cases and unexposed in others A dilution of exposure is thereby introduced into the

Table 2

Results of the atomic bomb genetic study when re analysed for the effect of one parent exposure. Significant genetic effects in the bombed population can be ascribed to irradiation in relation both to paternal exposure (neonatal deaths) and to maternal exposure (sex ratio and stillbirths). The ensemble of the data (total loss) is significant even when paternal exposure alone is considered. The unexposed population is not considered. Based on data in the ABCC Report

			Births	Index cases No.	Index cases %	χ^2	df	P
Sex ratio (males to total)	Father only exposed	lightly	3 670	1 892	51.55	0.68	1	—
		heavily	1 373	726	52.88			
	Mother only exposed	lightly	14 684	7 681	52.31	6.01	1	< 0.02
		heavily	4 608	2 324	50.43			
Malformations at birth	Father only exposed	lightly	3 670	28	0.763	3.35	1	—
		heavily	1 373	18	1.311			
	Mother only exposed	lightly	14 684	121	0.824	0.30	1	—
		heavily	4 608	42	0.911			
Stillbirths	Father only exposed	lightly	3 629	57	1.570	0.25	1	—
		heavily	1 354	24	1.772			
	Mother only exposed	lightly	14 547	216	1.484	4.67	1	~0.03
		heavily	4 561	89	1.951			
Neonatal deaths	Father only exposed	lightly	3 572	49	1.372	4.11	1	< 0.05
		heavily	1 330	9	2.180			
	Mother only exposed	lightly	14 331	217	1.514	*(0.16)	1	—
		heavily	4 472	64	1.431			
Pooled paternal and maternal exposure	Total loss					19.21	7	< 0.01
	Total loss excluding sex ratio loss					12.52	5	< 0.03
Paternal exposure only	Total loss					8.39	3	< 0.05
	Total loss excluding sex ratio loss					7.71	2	< 0.03

A highly significant difference

A significant difference

An insignificant difference in a direction contrary to the genetic hypothesis; this contribution to χ^2 is subtracted from the total

unexposed groups and vice versa this is undesirable in view of the genetic hypothesis that germ cells of both sexes are subject to mutagenic influences and especially serious in the case of the sex ratio upon which exposure of father and mother are expected to act in opposite directions (Fig 1). Fortunately the data in the report are presented in such a way that this objection can be removed and in the next paragraph a consideration shall be given to the apparent effect of the separate exposure of each parent. Further it is necessary to agree with NEEL and SCHULL that comparisons between groups com

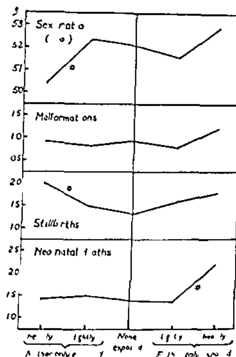


Fig. 3. Genetic effects of exposure to atomic detonations in Hiroshima and Nagasaki shown by a comparison of the offspring after light or heavy exposure of one parent (method of analysis discussed in text); see also Table 2. The parameters belonging to the unexposed population are shown in the mid line of the figure but are not taken into account in the discussion for reasons given in the text. Statistically significant differences ($p < 0.05$) are shown by asterisks. Based on new analysis of data from NEEL, SCHULL et coll. (Nat. Res. Counc. Publ. 461, 1956)

prising both unexposed and exposed are faulty, since the unexposed population, having been outside of either city at the time of the bombing, is a different population, most of which immigrated into the cities later. The validity of this doubt can be illustrated by the significantly different mean maternal age and parity in the unexposed and exposed, which have been calculated from the data in the report and are given elsewhere (DE BELLEFEUILLE 1960).

A set of comparisons is therefore in order between pairs of groups, each group of every pair differing only in that one parent has been exposed lightly, or heavily, the other parent having been unexposed in every case. The lightly exposed parent (exposure category 2) can be considered, for the present purpose, a virtually unexposed control, the dose of radiation being estimated in this class at 5 to 10 rep. The group of heavily exposed parents shall consist of all the other exposed, moderately or heavily according to the classes used in the report (categories 3, 4, 5 pooled). The validity of this type of comparison is shown by the fact that mean maternal age does not differ significantly in relation to light or heavy one parent exposure, either paternal or maternal (DE BELLEFEUILLE 1960). In contrast, there is a marked difference in mean parity (birth order) in relation to both pure paternal and maternal exposure; this, as discussed below, may well in itself reflect a genetic effect. One may safely assume, therefore, that one is dealing with equivalent populations, and glance at the result of the comparisons (Table 2). There is a well marked trend in the direction of the genetic hypothesis in 7 of 8 comparisons involving one parent exposure, and in 3 the difference is statistically significant for

maternal exposure toward the sex ratio and the incidence of stillbirths, and paternal exposure toward the incidence of neo natal deaths The same data are represented graphically in Fig 3 where the statistically significant effects are marked by asterisks

The comparisons outlined in Table 2 require some comment

1 Sex ratio This significant result of maternal exposure has been shown in the ABCC Report (p 92) it is in fact the only computation involving one parent exposure to be found therein The effect of paternal exposure, which is in the opposite direction though not significant statistically, is in accord with the genetic theory (Fig 1) More precisely as discussed by LEJEUNE and TURPIN (1957) male births are expected to regress from light paternal irradiation and to increase from massive exposure major aberrations in the X chromosome being postulated in the latter case As seen in Fig 3, just these tendencies are suggested in the atomic bombed population

2 Malformation at birth The trends are not significant statistically Some possible reasons for this suggest themselves What would seem at first sight to be a serious lack in the data collected is the omission of congenital heart and great vessel disease decided upon in the ABCC study because of unreliability of the diagnosis of such lesions at birth Although *granting the* latter point one might think, in view of the results of other studies, that this exclusion amounting to 97 cases would explain in part the negative result obtained However SCHULL (1959) reports an incidence of *congenital* heart disease of 1 60/1 000 births if the parents were unexposed 1 52/1 000 births if one or both parents were lightly exposed (radiation category 2) and 0 98/1 000 if one or both parents were moderately or heavily exposed (radiation categories 3, 4 or 5) Although the incidence in relation *to one* parent exposure cannot be computed from these data, it is almost certain that no marked effect would emerge Rather then the absence of a significant effect of parental exposure must come from the nature of *the material* surveyed We have seen that while the mothers who were exposed lightly did not differ significantly in mean age from those who were exposed heavily the latter showed a notably lower mean parity This means in effect that the more severely exposed mothers were *having their first* children (abortions not being taken into account) later than the others *This could* result from the exposure itself perhaps it was that the somatic effects on the general health or especially on the generative organs resulted *in these* women marrying or conceiving later or that chromosome aberrations *in ovarian* germ cells (especially likely due to neutrons ABCC Report p 51) rendered the heavily irradiated women temporarily sterile or caused them to conceive lethally malformed offspring which were eliminated early *Abortions* were not considered in the report, further it is admitted (p 100) that many malformed infants could have

been disposed of early, before coming to the knowledge of the enquirers The survey is concerned with major malformations diagnosed at birth, a sampling of the same population at the age of 9 months, however, showed that only 43 % of the *malformations known at that time to exist*, or to have existed, had been recognised at birth This fact, coupled with the limited duration of the study, which encompassed only 6 years of one generation, means that only a small fraction were studied of the births among which a genetic teratogenic effect of radiation might have been operative Still, as we shall see later, the data on congenital malformations are consistent with the expected magnitude of effect

3 Stillbirths On the incidence of stillbirths, it is maternal exposure which seems to have the most marked effect (Table 2, Fig 3) That the apparent effect of paternal exposure is not significant is due, doubtless, to an effect similar to that discussed *in the preceding paragraph namely, that heavy* paternal exposure is associated with a lower mean parity Because somatic effects on the father cannot be involved here, the whole effect must be genetic in nature Azoospermia due to roentgen rays has been known for a long time in rodents (ALBERS SCHONBERG 1903, BERGONIE & TRIBONDEAU 1904) and in man (HUHNER 1935) In the Japanese seamen on board the Fifth Fukuryu Maru ("Lucky Dragon") who were sprinkled with thermonuclear dust near Bikini, in 1954, heavy exposure to radio activity was followed by a long period of aspermia and infertility lasting many months (TSUZUKI 1956, p 1287) *It is plausible that in Hiroshima and Nagasaki, following heavy* irradiation of fathers, once recovery from temporary sterility had occurred, there were conceived a number of non viable foetuses which were eliminated early Such is the likely explanation for the fact that the mates of heavily-irradiated men bore their children later The same effect is shown in the ABCC Report when in a consideration of first born infants only it is found that the mothers of the stillborn infants were in the mean older than those of the liveborn, and this was especially marked in the *offspring of heavily* exposed fathers Because of this, the authors of the report disclaim the well *marked correlation, which they found, between* stillbirth rates in first born infants and paternal exposure, and go on to show that if the stillbirths are distributed into maternal age groups, the apparent effect of paternal exposure disappears

This disappearance, however, is wholly due to the breaking of the sample into small groups If, on the contrary, the same data are treated as a whole and corrected for maternal age, the highly significant relationship between paternal exposure *and incidence of stillbirths in first births* is conserved

4 Neo natal deaths It appears from Table 2 that exposure of the father alone was associated with a higher neo natal death rate, but not exposure

Table 3

Autopsy studies in the atomic bomb genetic survey One study (Nagasaki) shows a significant effect of irradiation while the other (Hiroshima) does not This disparity is seen to arise in a large measure from the difference in numbers involved these being smaller in the Hiroshima survey

	Total bodies	Abnormal bodies	χ	P
A *Hiroshima (ABCC Report)*				
Father only exposed	31	7 (22 6)	0 40	—
No parent exposed	211	37 (17.5)		
Mother only exposed	127	20 (15 8)	0 16	—
B *Nagasaki (Hayash)*				
Father only exposed	80	18 (22.5)	7.56	< 0 01
No parent exposed	363	40 (11 0)		
Mother only exposed	259	47 (18 1)	6 49	< 0 0?
At least one parent exposed within 2 km	72	20 (27 7)	5 14	< 0 03
At least one parent exposed but none nearer than 5 km	317	5? (16 4)		

(The unexposed population is excluded from the latter comparison)

of the mother alone Differences in anatomical shielding between male and female gonads may enter into consideration but it is surprising that maternal somatic effects do not seem to play a role here This perhaps may embolden us to discount the operation of any such somatic effect in the above discussed apparent connexion between maternal irradiation and stillbirth and increase the plausibility of the genetic nature of that effect

5 *Total loss* The data of the ABCC Report are given in such a way that offspring showing a given accident are removed from the group to be considered for the next accident for instance as inspection of the figures in Table 2 will show the malformed children are removed from the number to be considered for stillbirth etc Thus each child who might constitute an indicator of genetic factors is considered but once This makes it permissible to summate the total effect, as seen in the incidence of malformations at birth stillbirths and neo natal deaths and in the sex ratio changes, as an index of the total reproductive failure As seen in Table 2 the statistical evaluation of this summation yields a result which is highly significant in favour of the hypothesis of a genetic ill effect of radiation The notion of a wastage of offspring reflected by changes in the sex ratio rests upon the assumption that the lowering of the sex ratio in the mother only exposed group is due to the loss (through early absorption or abortion) of a certain number of males,

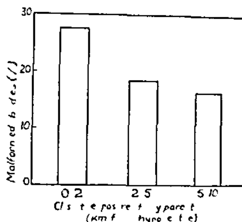


Fig 4 Autopsy study of peri natal deaths in Nagasaki (1949—1953) The proportion of seriously malformed bodies varies significantly with the distance from the detonation hypocentre The unexposed population is excluded from this comparison Based on data from HAYASHI (1956) See also Table 3

and the raising of the sex ratio in the father only exposed group is due to a *loss of females* (Fig 1) Should one like to question the validity of this assumption, a total loss value (excluding sex ratio losses) can still be shown to be significant at the 3 % level A summation of the data on paternal exposure alone (where somatic effects cannot be predicated) is also significant, whether or not *the sex ratio changes are taken into account* (Table 2)

The ABCC Report also presents data of 406 autopsies done in Hiroshima, from May 1949 to December 1953, on infants stillborn or dying in the first 6 days of life, all were the product of at least 21 weeks' gestation They represented 62 % of all deaths occurring in newborns registered in the study The incidence of malformations in the autopsied bodies (including this time, congenital cardiovascular disease) is distributed in groups on the basis of exposure *or non exposure of each or both parents A difference appears in* the incidence of anomalies, but it is not significant (Table 3 A) No information is given in the report on the frequency of various types of malformations found in the groups

Autopsy data in Nagasaki Independently of the ABCC survey, which we have reviewed in the preceding paragraphs a series of autopsies on 884 foetuses and newborns was studied by I Hayashi, Professor of Pathology in Nagasaki University, from September 1949 to December 1953 Since the data pertaining to this work are not available in any detail in non Japanese literature the report (HAYASHI 1956) is summarized here at some length All anomalies found are listed with their distribution in the exposed and the non exposed classes Some common minor anomalies such as accessory spleen, Marchand s accessory adrenal glands reverse position of the sigmoid, mobile caecum, intrusion of the pancreas into the small intestine, and abnormal lobation of the lungs, are not taken into account The malformations which were retained show a significant relation to both paternal and maternal exposure (Table 3 B) when the incidence of abnormal bodies in the father only and the mother

only exposed groups is compared with that in the no-parent exposed group. As to the types of malformations, diaphragmatic hernia and complex malformations of the heart and great vessels were more frequent in the exposed group. Some anomalies were seen only in the exposed group including meningeal cyst (2 cases), atresia ani (3 cases) and atresia choledoci (2 cases). HAYASHI states that the histories of all mothers are being reviewed in order to rule out the operation of any factor, other than exposure which could explain the differences found. This has been done for the cases of malformations of the heart and great vessels which were found to bear no relation to sex, living birth, stillbirth, miscarriage, premature birth, normal birth, position in pregnancy, life duration after birth, season of conception, time of birth, mother's age, difference between father and mother, menstrual habit of mother, history of parents other than that of exposure, serological test, intermarriage and numbers of pregnancy after exposure. However the mothers who bore offspring with cardiovascular anomalies in 9 instances out of 12 had had abortion or miscarriage within the preceding year.

Here then are two reports on the autopsy incidence of congenital malformations in populations exposed to atomic bombs prior to conception. One survey based on the findings in Hiroshima fails to show an affect of radiation; in the other from Nagasaki a strong statistical suggestion is found in favour of the mutagenic effect of atomic radiation. It is true that the latter study, that of HAYASHI, deals with twice as many cases as the former. It is also possible that the different types of radiations (more gamma, fewer neutrons in Nagasaki) and the dissimilar climatic conditions in the two cities at the time of the explosions may account in part for the disparity. Nevertheless the authors of the ABCC Report who claim to have records on 363 autopsies in Nagasaki (which they fail to publish) question the validity of Hayashi's data and suggest rather gratuitously that a bias may create a spurious correlation. They claim for instance that the control figure (11.0 %) for the incidence of abnormal bodies from unirradiated parents is too low. However it is a simple matter to compute from Hayashi's data the incidence of abnormal bodies in relation to distance from the hypocentre (Fig. 4), the comparison which excludes the unexposed controls yields a significant difference at the 3 % level (Table 3 B). This would seem to dispose of the doubts referred to above.

Addendum

W. L. RUSSELL's (1960) latest results of chronic low-dose gamma irradiation of mouse spermatogonia support the prediction that no threshold dose below which no genetic effect is incurred would be demonstrable. While confirming the dependance which his 1958 work had indicated of the magnitude of effect on the dose rate, RUSSELL now fails to find a further reduction of the effect when the dose rate is decreased below 90 r per week; indeed at 10 r/week the mutagenic effect per unit of radiation is no less marked than at 90 r/week. A dose of 86 r given at the rate of 10 r/week produces a highly significant increase in mutations

SUMMARY

Experimental, clinical and epidemiological data which have a bearing on the definition of the genetic risk to man from ionizing radiations have been reviewed. Through a new analysis of the official Report of the U. S. Commission of enquiry in Hiroshima and Nagasaki based on a consideration of the irradiation of each parent separately, the probability of a harmful genetic effect in the first generation born to persons exposed to the atomic bombs in 1945 is demonstrated. The total effect, as manifested by altered sex ratio, congenital malformations and peri-natal mortality, is significant even when one considers only the exposure of fathers, in whom somatic changes cannot contribute to the observed effect. Autopsy evidence for the teratogenic effect of atomic radiations is also reviewed. The significance of these data in relation to the expected mutagenic effect on man of actual and possible loads of ionizing radiations will be discussed in Part II.

ZUSAMMENFASSUNG

Experimentelle, klinische und epidemiologische Daten, die mit der Definition des genetischen Risikos des Menschen gegenüber ionisierender Strahlung im Zusammenhang stehen können, sind nachgeprüft worden. Durch eine neue Analyse des offiziellen Rapportes der amerikanischen Untersuchungskommission in Hiroshima und Nagasaki, welche sich auf die Betrachtung der Bestrahlung von Eltern separat gründen, wird die Möglichkeit eines schädlichen genetischen Effektes in der ersten Generation von Kindern nachgewiesen, die von Personen geboren wurden, welche der Atombombenbestrahlung 1945 ausgesetzt waren. Der totale Effekt, manifestiert durch eine veränderte Geschlechtsratio, kongenitale Missbildungen und perinatale Tödlichkeit, ist signifikant, auch wenn man nur die Exponierung der Väter in Betracht zieht, bei denen somatische Veränderungen nicht zu dem beobachteten Effekt beitragen können. Der anatomische Nachweis des teratogenen Effektes der Atomstrahlung ist ebenfalls nachgeprüft worden. Die Signifikanz dieser Daten in Beziehung zu dem erwarteten mutagenen Effekt beim Menschen durch aktuelle oder mögliche Strahlenbelastung wird in Teil II diskutiert.

RÉSUMÉ

Revue critique des données expérimentales, cliniques et épidémiologiques permettant de préciser le risque génétique pour l'homme des rayonnements ionisants. Une nouvelle analyse du Rapport officiel de la commission américaine d'enquête à Hiroshima et Nagasaki, où l'on considère séparément l'irradiation de chaque parent, permet de démontrer la probabilité d'un effet génétique défavorable à la première génération issue de parents exposés aux bombes atomiques de 1945. L'effet global, qui se manifeste dans le rapport des sexes, les malfaçons congénitales et la mortalité para-natale, demeure significatif même si l'on ne considère que l'irradiation des pères, chez qui on ne saurait invoquer d'altération somatique. On rapporte enfin les preuves anatomiques de l'effet tératogène des rayonnements atomiques. La signification de ces données quant à l'effet mutagène attendu des doses actuelles et possibles de rayonnements ionisants fera l'objet d'une deuxième partie de cette étude.

REFERENCES

For a complete bibliography see Part II which will appear in next number of Acta radiologica 56 (1961) 145.

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ANGIOGRAPHY IN CARCINOMA OF THE RENAL PELVIS

by

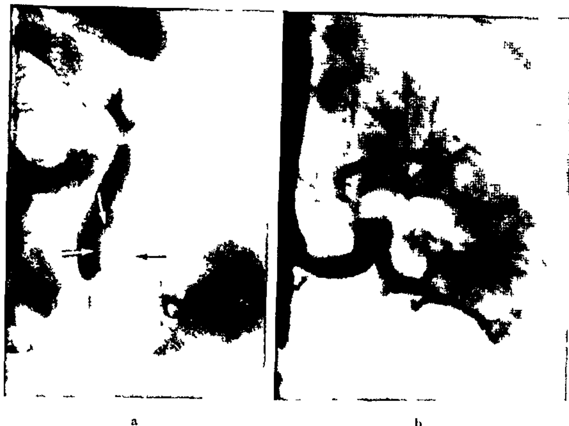
ERIK BOIJSEN and JOHAN FOLIN

Renal angiography has during the last decade constituted a routine diagnostic procedure affording invaluable information on various conditions of disease Furthermore accumulated experiences of the method have considerably in creased our knowledge of the normal and pathologic roentgen appearances of the renal vascular system

The great value of renal angiography in tumors invading the renal paren chyma is indisputable It is generally held however that carcinoma of the renal pelvis is avascular and never produces characteristic angiographic appearances (NELSON 1942 DOSS 1946 SHAPIRO 1953 CREEVY & PRICE 1955 RICHES 1955, 1959 EDSMAN 1957 EVANS 1957) If the tumor is located in the intrarenal part of the pelvis and infiltrates the parenchyma the vessels within the infiltrated region have a reduced caliber and are displaced and an irregular defect is produced in the nephrographic phase (DOSS EDSMAN) tumor vessels have been observed in a few cases of infiltrating renal pelvic carcinoma (PIRONTI & TARQUINI 1958 GREGG 1958 VOGLER & HERBST 1958)

If the tumor lies in the confluent part of the renal pelvis the angiographic appearances may be the same as in advanced hydronephrosis viz indicate a markedly reduced blood supply and displaced vessels (RUNSTROM 1948 PALMLOV 1952 WEYDE 1952 MORINO & TARQUINI 1957, EDSMAN PIRONTI &

From the Roentgendiagnostic Department (Director Prof Olle Olsson) University of Lund Sweden Submitted for publication 30 January 1961



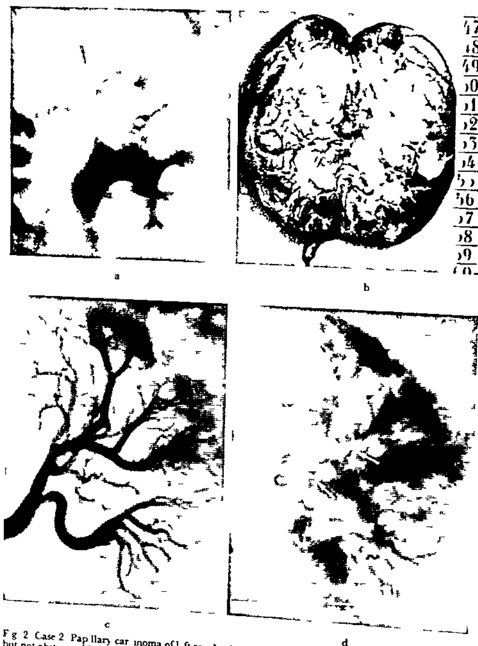
a b

Fig. 1. Case 1. Papillary carcinoma of left renal pelvis. a) Urography: small tumor in lower part of pelvis. b) Aortic renal angiography: normal findings.

Tarquini inter al.). A 'silent' kidney may be found at urography and the tumor of the kidney pelvis revealed at pyelography; these methods have thus been considered those of choice in the diagnosis of renal pelvic tumors (Creevy & Price, Plotfgher 1957, inter al.).

The angiographic appearances of the vessels supplying the renal pelvis and upper ureter have been previously described (Boijsen 1959). Normally these vessels are too minute to be visible during angiography. In two of three cases of renal pelvic carcinoma pathologic vessels arising from a displaced and widened pelvoureteric artery could however be seen at selective renal angiography. Our own experiences of the angiographic characteristics of renal pelvic tumors are now reported.

Material. Ten cases of unilateral renal pelvic tumors were examined by renal angiography. Of these, 8 were proved histologically after nephrectomy (7) or autopsy (1). Two cases were not subjected to operation and therefore not verified, but both had histologically proved carcinomas of the bladder and these were presumed to represent metastases from angiographically malignant tumors of the kidneys. Two of the histologically proved renal pelvic tumors were



F g 2 Case 2 Pap llary car inoma of l ft renal pel is a) Urography upper ramus of pel is d tended but not obstru ted by tumo b) Operat on specimen, small tumor in upper part of renal s nus normal p r nchym) and d) S l ctive nal angiography normal vascularizat on of renal parenchyma Late in the arterial phase (d) a wide and tortuous pelvic artery (→) supplies the tumo



Fig 1 Case 1 Papillary carcinoma of left renal pelvis a) Urography small tumor in lower part of pelvis b) Aortic renal angiography normal findings

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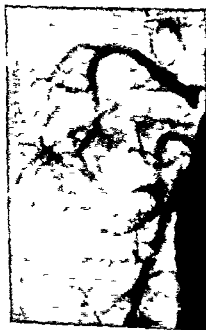
Material Ten cases of unilateral renal pelvic tumors were examined by renal angiography Of these, 8 were proved histologically after nephrectomy (7) or autopsy (1) Two cases were not subjected to operation and therefore not verified, but both had histologically proved carcinomas of the bladder and these were presumed to represent metastases from angiographically malignant tumors of the kidneys Two of the histologically proved renal pelvic tumors were



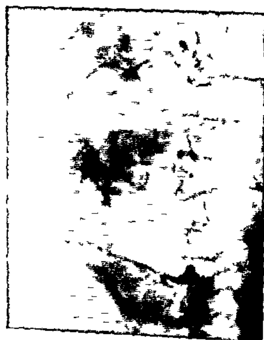
a



b



c



d

Fig 3 Case 4 Papillary *carcinoma* of right renal pelvis infiltrating parenchyma a) Urography tumor bulging into right pelvis of a horseshoe kidney no obstruction to urinary outflow b) Operation specimen c) and d) Aortic *renal* angiography tumor vessels arising from peripheral branches of main renal artery supply the tumor

combined with bladder growths and two with ureteric tumors, all of the same type as in the renal pelvis The ages of the patients ranged from 44 to 73 years

It is possible from a roentgendiagnostic and especially from an angiographic point of view to divide the present collection of renal pelvic tumors into three groups The *first* group is represented by a small renal pelvic tumor in a normally functioning kidney, in the *second* group the renal pelvic tumor infiltrates the renal parenchyma, and the *third* group is characterized by a renal pelvic tumor obstructing the urinary outflow and causing complete or localized hydronephrosis

Case reports

Cases belonging to group I

Case 1 Male, aged 60 with intermittent haematuria for six months *Urography* Tumor, 1 cm in diameter at base of left renal pelvis *Aortic renal angiography* Normal left renal artery and branches normal accumulation of contrast medium in renal parenchyma *Cystoscopy* Tumor on right side of bladder *Operation* Resection of the tumors of left renal pelvis and bladder *Pathology* report Both tumors differentiated papillary carcinomas no infiltration

Case 2 Male aged 64 with abdominal pain for a week and haematuria (microscopy) *Urography* A 2 by 3 cm irregular tumor in upper part of left renal pelvis *Selective left renal angiography* Renal artery and branches not displaced A tortuous irregular artery branching from the dorsal artery supplied the tumor Normal accumulation of contrast medium in renal parenchyma *Operation* Ureteronephrectomy *Pathology* report Large differentiated papillary tumor distending upper part of renal pelvis No infiltration of renal parenchyma

Comments

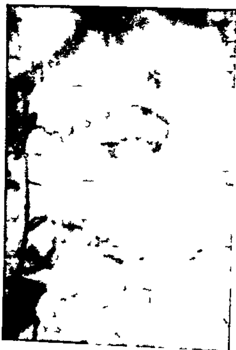
Small kidney pelvic tumors in a normally functioning kidney may easily be diagnosed by urography As long as the growth is small is confined to the intrarenal part of the pelvis and does not infiltrate the parenchyma it is supplied by the small renal pelvic vessels that arise from the primary branches of the renal artery These fine vessels are increased in width when supplying a tumor but are in our experience too small to be seen at aortic renal angiography (Case 1) Selective renal angiography may however because of the higher density of the contrast medium show a widened tortuous renal pelvic artery supplying the tumor (Case 2) Irrespective of which type of angiography is chosen no tumor vessels will be demonstrated as long as the renal parenchyma is intact

Cases belonging to group II

Case 3 Female aged 73 with a four year history of right loin pain and haematuria *Urography* Upper part of right kidney widened with no excretion evident in this region the remainder of the kidney functioned normally Ramus of upper calyx abruptly cut off *Aortic renal angiography* The right renal artery was slightly reduced in width The intrarenal branches in the upper half of the kidney were slightly narrowed somewhat sparse but not displaced A tortuous vessel running inwards and downwards represented a widened pelvo ureteric artery No tumor vessels present but in the upper half of the kidney the contrast medium accumulated irregularly with no demarcation between the cortex and the medulla as in the lower half Patient was not operated upon and died 9 months later *Postmortem examination* Anaplastic solid carcinoma arising from upper part of right renal pelvis infiltrating the parenchyma and extending distally around the lower part of the renal pelvis and upper part of the ureter Metastases in the abdomen and lungs



a



b



c

F g 5 Case 6 Pap llary carcinoma of left renal pelvis and u eter

a) and b) Aort c renal ang ography reduced blood supply to enlarged l ft k dney with irregular lateral contou w dened ur teropelv c artery (→) an be followed d stally and pathologic v ssels are seen within its region of supply Tumor vess ls a ising f om the w dened pelvic vessel are also evident in the central part of the kidney

c) Arteriography of operat on spe imen showing sam appearances Urete opel c a tery w dened down to th site of the tumo in the ur ter

Case 4 Male aged 61 with right loin pain and intermittent haematuria for one month *Urography* Horse shoe kidney with irregular calcifications in the central part of the right lobe medial to the calcifications a tumor, 3 × 4 cm in size, bulged into the confluent part of the renal pelvis *Aortic renal angiography* Right kidney supplied by two vessels of normal width irregular vessels as well as accumulation of contrast medium evident within the tumor shown at urography *Operation* Nephrectomy *Pathology* report Differentiated papillary pelvic tumor about the size of a walnut arising from a middle calyx and bulging into the renal pelvis Renal parenchyma infiltrated at the base of tumor

Comments

If the tumor arises in the intrarenal part of the renal pelvis and infiltrates the parenchyma a primary carcinoma of the latter cannot be excluded as urography pyelography as well as angiography may produce the same appearances in both types of carcinoma When a renal pelvic carcinoma grows into the parenchyma the infiltrating part of the tumor is supplied by the peripheral branches of the renal artery If a renal carcinoma bulges or infiltrates into the kidney pelvis this part of the tumor is supplied by the more centrally placed fine renal pelvic vessels If no tumor vessels are evident in an infiltrating renal pelvic carcinoma there will be an irregular accumulation of medium within the infiltrated region and no demarcation between the cortex and the medulla just as in a renal carcinoma



Fig 4 Case 5 Papillary carcinoma of left renal pelvis and upper ureter Aortic renal angiography renal artery and branches small and displaced widened ureteropelvic artery (→) arising from dorsal artery supplying the tumor with pathologic vessels No accumulation of medium in parenchyma

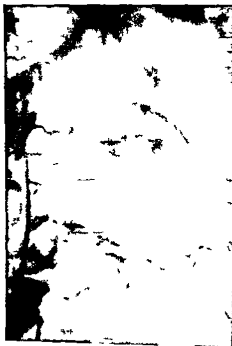
Cases belonging to group III

Case 5 Male aged 59 with loss of weight and lassitude for six months *Urography* Enlarged kidney with irregular surface no evidence of excretion *Aortic renal angiography* Narrowed left renal artery with very small and displaced branches The ureteropelvic artery arose from the distal branch of the dorsal artery turned inwards and downwards and was wider than the parent branch small tumor vessels were evident in the region it supplied *Operation* Ureteronephrectomy *Pathology* report Differentiated papillary tumor at ureteropelvic junction with small growths in upper part of ureter No infiltration into parenchyma

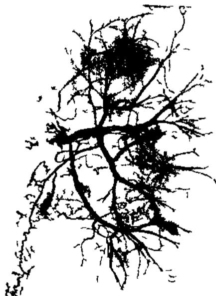
Case 6 Female aged 56 with haematuria for three weeks *Urography* Somewhat enlarged nonfunctioning left kidney with irregular surface *Aortic renal angiography* Markedly narrowed left renal artery with branches and the intrarenal branches displaced and giving rise centrally to pathologic vessels A wide ureteropelvic artery from the dorsal artery supplied a tumor with pathologic vessels *Pyelography* Irregular tumor within renal pelvis and upper ureter marked peripheral hydronephrosis *Operation* Ureteronephrectomy *Pathology* report Peripheral



a



b



c

Fig 5 Case 6 Papillary carcinoma of left renal pelvis and ureter

a) and b) Aortic renal angiography reduced blood supply to enlarged left kidney with irregular lateral contour widened ureteropelvic artery (→) can be followed distally and pathologic vessels are seen within its region of supply Tumor vessels arising from the widened pelvic vessels are also evident in the central part of the kidney

c) Arteriography of operation specimen showing same appearances Ureteropelvic artery widened down to the site of the tumor in the ureter



Fig 6 Case 7 Papillary carcinoma of right renal pelvis a) and b) Selective renal angiography enlarged kidney narrowed renal artery and branches displaced by large tumor A middle capsular artery (←) is displaced by the tumor A widened and displaced ureteropelvic artery (←↑) supplies the tumor with pathologic vessels and widened pelvic arteries supply the intrarenal part of the tumor

hydronephrosis with much reduced parenchyma Advanced papillomatous changes in upper part of ureter and central part of renal pelvis Poorly differentiated papillary carcinoma rich in vessels

Case 7 Male aged 44 with intermittent haematuria and right loin pain for two years *Cystoscopy* Two large papillomatous tumors in bladder *Urography* Non functioning enlarged right kidney with irregular lateral surface *Pyelography* Confluent part of the right renal pelvis deformed by a tumor Normal ureter *Selective renal angiography* Right renal artery and its branches narrowed and markedly displaced Pathologic vessels evident centrally in the enlarged kidney and arising medial to the kidney from widened ureteropelvic artery a capsular artery was greatly displaced by the tumor No accumulation of medium within the renal parenchyma *Operation* Ureteronephrectomy and removal of bladder growths *Pathology report* *Differentiated papillary tumor about 10 × 5 cm in size in right renal pelvis gross* hydronephrosis Renal parenchyma reduced to a thin layer Infiltration of tumor into surrounding fatty tissues and into lymphatics Vesical tumors of the same histologic type as renal pelvic tumor

Case 8 Male, aged 61, with left colicky pain for four months and slight haematuria for one month *Urography* Large tumor in upper part of left kidney obliterating upper calyces and displacing remainder of renal pelvis downwards *Aortic renal angiography* An artery of normal

caliber supplied the lower pole and a narrowed artery the remainder of the kidney the intra renal branches of the latter were narrowed and displaced A large number of small tumor vessels were evident in the upper half of the kidney late in the arterial phase Normal accumulation of contrast medium in lower pole with differentiation between the cortex and the medulla practically no medium evident in remainder of kidney *Operation* Nephrectomy The kidney appeared normal apart from slight enlargement of its upper pole Ureterectomy not performed as there was no macroscopic evidence of renal pelvic carcinoma *Pathology* report Differentiated papillary tumor at upper part of renal pelvis displacing and reducing the parenchyma to a thin layer No infiltration into parenchyma

Comments

All of the proved cases of tumor at the ureteropelvic junction had a urographically silent kidney which was enlarged and had an irregular surface Thus urography cannot give a definite diagnosis of renal pelvic carcinoma Only in one of the cases was it possible to demonstrate a papillary tumor by pyelography

Renal angiography on the other hand in all three cases produced conclusive evidence of a renal growth causing obstruction The signs were as follows (1) A markedly reduced vascular supply to an enlarged kidney and displacement of the central branches of the renal artery by the tumor in the confluent part of the renal pelvis (2) A wide ureteropelvic artery supplying the tumor with pathologic vessels medial to the kidney (3) Because of the reduced parenchyma and the growth of the tumor practically no contrast medium accumulated in the nephrographic phase (4) Due to the advanced atrophy of the renal parenchyma tumor vessels arising from widened pelvic arteries were evident late in the arterial phase within the intra renal part of the renal pelvis

If the renal pelvic carcinoma arises within a ramus of the renal pelvis and causes a localized pressure atrophy of the parenchyma the angiographic appearances will be similar but confined to only a part of the kidney (Case 8) A widened ureteropelvic artery will not be apparent because the tumor is not within its field of supply

Discussion

Three types of renal pelvic carcinoma could be differentiated in the present investigation

Small tumors of the renal pelvis which do not infiltrate the renal parenchyma (group I) may be demonstrated at urography but for the final diagnosis renal angiography may provide supplementary information of great value No tumor vessels or accumulation of contrast medium within the tumor will be evident as in the first place the tumor vessels in a renal pelvic carcinoma are narrow and sparse and secondly the accumulation of medium in the unaffected renal parenchyma will hide these fine vessels

Infiltrating carcinoma of the renal pelvis (group II) cannot be differentiated from renal carcinoma of low vascularization either by urography or renal angiography Three tumors were of the infiltrating type in the present material One of these was not verified (Case 9) but at cystoscopy a biopsy was made of a large bladder growth which histologically had the characteristics of a vesical carcinoma and a malignant tumor in the right kidney was demonstrated by renal angiography Thus, in all three cases a diagnosis of carcinoma was

made although it was not possible to state that the tumor arose from the renal pelvis. Two of the cases had tumor vessels arising from the peripheral branches of the renal artery and a wide ureteropelvic artery supplied the tumor, though rare, a renal carcinoma may in fact be supplied by a ureteropelvic artery (BOIJSEN). If, on the other hand, the tumor arises from the upper part of the ureter or from the extrarenal part of the renal pelvis it is always supplied by the ureteropelvic artery, which will be filled at renal angiography. Of the 10 cases of renal pelvic tumors a wide ureteropelvic artery was evident in 6, that is in all cases in which the tumor arose or extended medial to the kidney.

From a surgical point of view the diagnosis of renal pelvic carcinoma is important because ureteronephrectomy should then be performed. If the diagnosis is not clear preoperatively it is usually impossible to decide the tumor type during the operation (O'CONOR 1956, TAYLOR 1959, inter al.), and the ureter will not be removed, with all the attendant risks. This is especially true when the tumor causes hydronephrosis, i.e. is of the same type that is difficult or impossible to diagnose by urography or pyelography.

Contrary to previous conceptions renal angiography offers the most important contribution to the diagnosis when the renal pelvic growth obstructs the urinary outflow (group III), and it is furthermore safe and conclusive. In 5 of the 10 cases there was a total (4) or a local (1) hydronephrosis with resultant advanced pressure atrophy and in only one of these was it possible by means of urography or pyelography to establish a correct diagnosis. One case was not histologically proved (Case 10), but the patient had a verified vesical carcinoma and the angiographic characteristics were the same as in the proved tumor cases causing hydronephrosis.

Previous authors have stated that hydronephrosis caused by a tumor of the renal pelvis cannot be distinguished from other types of hydronephrosis unless tumor vessels are shown. Such vessels may, according to these authors, be demonstrated only in a few cases and then only when there is infiltration of the parenchyma. In the present material, however, tumor vessels were observed in all cases in which a reduction of the parenchyma due to pressure atrophy was present. The pathologic vessels are always small and sparse, and arterio-venous shunts, so often seen in renal carcinoma, are only seldom observed. These fine tumor vessels within the kidney region can therefore only be observed when the angiography is of very 'high quality' and preferably performed as a selective study, and when there is advanced atrophy of the renal parenchyma. As in all cases of advanced pressure atrophy of the renal parenchyma the renal artery is small and the intrarenal branches displaced. This *combination of small and displaced renal arteries and tumor vessels will establish a diagnosis of renal pelvic carcinoma.*

Other characteristic changes may be observed at angiography and serve as confirmation of the diagnosis of a growth obstructing the renal pelvis, thus the tumor vessels arise early from the branches of the renal artery because they

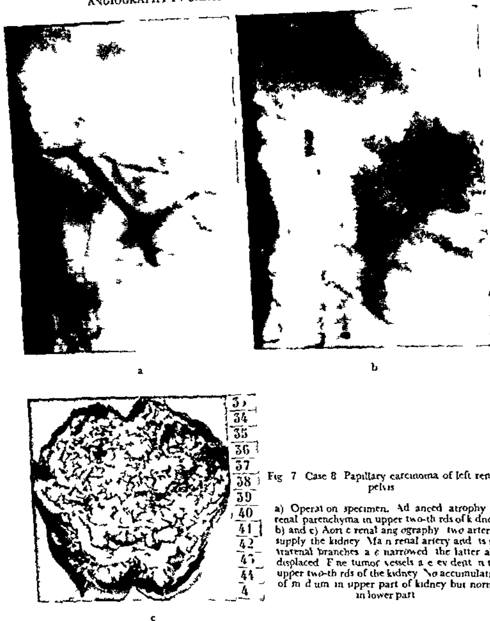


Fig 7 Case 8 Papillary carcinoma of left renal pelvis

a) Operation specimen. Advanced atrophy of renal parenchyma in upper two-thirds of kidney b) and c) Aortic renal angiography two arteries supply the kidney Main renal artery and its intrarenal branches are narrowed the latter also displaced Fine tumor vessels are evident in the upper two-thirds of the kidney No accumulation of medium in upper part of kidney but normal in lower part

branch from the intrarenal pelvic arteries and not from the peripheral branches as in renal carcinoma

The width of the renal artery corresponds closely to the reduction of the parenchyma in the common type of hydronephrosis (IDBOHRN 1956 WIDEN

1958) and there is an accumulation of contrast medium in the parenchyma so that a distinction between the cortex and the medulla is possible The marked narrowing of the renal artery in the present tumor cases indicated that only a thin layer of renal parenchyma was present, this layer was, however, even thinner than might have been expected with such a small renal artery because the tumor was supplied by the same vessel There was therefore hardly any accumulation of medium in the parenchyma and the cortex and the medulla could not be differentiated

Another important difference between hydronephrosis caused by a tumor and true hydronephrosis is the size of the ureteropelvic artery, the widened ureteropelvic artery and the small dorsal artery bear a relationship which is never observed in hydronephrosis not caused by a tumor

SUMMARY

Ten cases of carcinoma of the renal pelvis studied by renal angiography are reported The characteristic angiographic appearances produced when the tumor obstructs the urinary flow are described

ZUSAMMENFASSUNG

Zehn Fälle mit Nierenbeckenkarzinomen welche mit einer renalen Angiographie untersucht worden sind werden berichtet Das für einen Tumorverschluss des Harnabflusses charakteristische angiographische Aussehen wird beschrieben

RÉSUMÉ

Les auteurs présentent dix cas de cancer du bassinet rénal étudiés par angiographie rénale Ils décrivent les images angiographiques caractéristiques obtenues quand la tumeur obstrue les voies urinaires

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Urography
Films obtained at 1 2 3 and 5 min intervals after commencement of injection of Hypaque



a) At 1 min Bilateral nephrograms



b) At min Contrast medium in calyces pelvis and upper part of ureter on left side Right kidney in nephrographic phase



c) At 3 min Still some difference in function between the two kidneys



d) At 5 min Differentiation between the function capacities of the kidneys now no longer possible

FROM VETERANS ADMINISTRATION HOSPITAL, LONG BEACH 4, CALIFORNIA, U S A

DIFFERENTIAL RENAL FUNCTION IN GOLDBLATT TYPE OF HYPERTENSION

Report of a case

by

RICHARD L SIGGERS

SQUIRE and SCHLEGEL in 1959 reported that urography was ineffective in the investigation of the differential renal function in renal hypertension Their films were obtained at 5 minutes after commencement of the injection

It occurred to the present author that the films in the above mentioned investigation had possibly not been obtained early enough, and for that reason a series of 100 normal patients were run in for study A timing mechanism was started immediately after the beginning of the injection and films were obtained at 1 min, 2 min, 3 min, 4 min, and 5 min It was noted that in normal patients the kidneys always functioned at the same time, the nephrographic phase occurring at 2 min and the pyelographic phase generally at 3 min In hypertensive patients, the pyelographic phase could generally be seen at 2 min and was always present bilaterally The hypothesis was advanced that in Goldblatt kidney there would possibly be a differential function due to renal artery insufficiency, and this was subsequently proved to be true

Case report

A 41 year-old man was admitted in our hospital in May 1960 for hypertension of four years duration Physical examination disclosed no definite cause of the hypertension The blood pressure was 220/110 mm Hg in the right and left arm and 300/1[illegible]5 mm in the right leg in the recumbent position The eyes showed minimal arteriolar narrowing The peripheral pulse equal and strong

Submitted for publication 15 March 1961

Laboratory examination Hemogram normal, urine analysis negative BUN 22 mg % fasting blood sugar 64 mg %, serum potassium 4 5 mEq/l with chlorides 105 mEq/l and sodium 1 37 mEq/l with bicarbonate 25 mEq/l Twenty four hour urinary catecholamines were 2 gamma per cent The regetine test and urinary culture were negative The Fishberg concentration test revealed a maximum concentration of 1 017 The serum creatine was 0 9 mg %

Roentgen examination of chest Marked left ventricular hypertrophy with congestive failure *Urography* In the 2 min film the right kidney remained in its nephrographic phase whilst the calyces, infundibula and pelvis of the left kidney were filled The 3 min film still showed a *differential* excretion between the two kidneys while in the 5 min film the function between the two kidneys was almost equal *Aortography* Marked stenosis of the right renal artery with post stenotic dilatation

At operation Arteriosclerotic plaque (of the right renal artery described by the pathologist as a *hyaline chondroid plaque*) *The blood pressure fluctuated during the postoperative* period and five months later averaged 140/90 mm Hg The patient is now asymptomatic

At a repeat examination five months after the operation, urography with 1, 2, 3, 4, and 5 min films *after the injection of the contrast medium it* was shown that there was equal function of the two kidneys

SUMMARY

A case of renal hypertension due to unilateral renal artery disease is presented A diagnosis of decreased renal function was suggested by the differences in function observed between the two kidneys in films obtained at 1 min, 2 min, and 3 min after the injection of contrast medium

ZUSAMMENFASSUNG

Ein Fall mit renalem Hochdruck bedingt durch einseitige Nierengefässerkrankung wird vorgelegt Die Diagnose einer herabgesetzten Nierenfunktion wurde durch die Unterschiede gestellt, welche man auf Röntgenbildern nach einer Minute sowie nach zwei und drei Minuten zwischen den beiden Nieren beobachtete

RÉSUMÉ

L auteur présente un cas d hypertension rénale due à une affection unilatérale d une artère rénale C est la différence observée entre les deux reins sur les films pris au bout d une de *deux et de trois minutes* qui a fait penser au diagnostic de diminution de la fonction rénale

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF OLLE OLSSON), UNIVERSITY OF LUND SWEDEN

ARTERIAL COMPLICATIONS IN THORACIC OUTLET COMPRESSION SYNDROME

by

TORD OLIN

The subclavian artery and the brachial plexus in their passage through the cervical region come to lie between the scalenus anterior and the scalenus medius and the first rib. The subclavian vein lies in front of the scalenus anterior but runs more or less parallel to the artery (Fig 1).

Maladjustment between the thoracic outlet and the plexus or vessels may result in compression of the latter with consequent symptoms. Such compression may be produced by unnatural positioning of the arm or by the presence of a rudimentary or cervical rib. The symptom complexes produced by such compression are called the cervical rib syndrome, the scalenus anterior syndrome, the costoclavicular syndrome, the compression syndrome and the hyperabduction syndrome, according to the presumed aetiology in a given case. It appears that the best blanket term for all these conditions is the one suggested by ROB & STANDEVEN (1958), viz the thoracic outlet compression syndrome. Complications caused by compression of the brachial plexus and the subclavian vein fall beyond the scope of the present investigation and will not be discussed.

Cervical ribs were first mentioned by GALEN and among those to contribute to our knowledge of such ribs were HUNAULD (1742) and particularly GRUBER (1849) (see KEEN 1907). The literature on the anomaly has since become

Submitted for publication 16 January 1961





PHILIPS

symmetrix 90-90





90° Trendelenburg   Sliding tabletop, ample range   Serial changer travels full length of table (108 cm)   All provisions for image intensification and X ray television   Ample protection against scatter radiation







Fig ? Case 1 a) Arteriography Catheter n r ght carotid artery Good fill ng of tortuous innominate a t ry common carot d artery and first p rt of subclavian artery Carotid artery manually compressed Large cervical ib on right s de b) Subcla ian artery occluded immed ately d stal to the origin of internal mammary and verteb al arteries Several collaterals especially f om the w dened internal mammary artery pass out into the arm

in a retrograde d rection into the innominate artery 15 ml Urografin 60 % were injected by a pressure syringe and serial films obtained During the injection the right carotid artery was compressed manually to minimize the flow of the contrast medium into the brain The innominate artery and the first part of the subclavian artery were widened and tortuous The subclavian artery was occluded by a thrombus immediately distal to the origin of the internal mammary and vertebral arteries and the thyrocervical and costocervical trunks All of these vessels except the vertebral artery gave off numerous collaterals to the arm Contrast medium from the collaterals had filled a small sl t in the axillary artery but otherwise the large artery supplying the arm was packed with thrombi and emboli

Phlebography No evidence of abnormality

Operation The scalenus anterior was divided and the compressed subclavian artery dissected. A small incision was made in the vessel and parts of the thrombus were aspirated until arterial blood flowed out in a retrograde direction The skin temperature of the hand was higher after the operation the pain disappeared and the arm muscles were no longer so weak

Case 2 Female aged 37 housewife had had numbness a feeling of cold and sensory loss of the right arm especially on the ulnar aspect for six months On admission the small muscles innervated by the ulnar nerve were atrophied The right radial pulse was weak and the blood pressure in the right arm was 25 mm Hg lower than that in the left The little and ring fingers were cold

Roentgen examination No changes in the cervical spine or the right shoulder

Angiog aphy of the right subclavian artery (Fig 3) An opaque catheter was introduced into the right femoral artery and advanced into the innominate artery to the opening of the right subclavian artery 15 ml Hypaque 45 were injected and serial films obtained The subclavian artery proved to be occluded immediately distal to the origin of the internal mammary

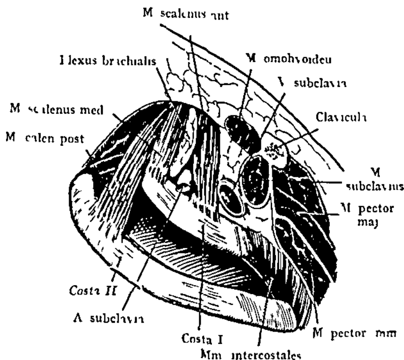


Fig 1 Drawing of thoracic outlet on right side (from CORNING)

voluminous In 1818, COOPER & TRAVERS treated the symptoms produced by cervical ribs by conservative methods but the first to report a successful operation in such a case was COOTE (1861), (see EDEN 1939—40), the subclavian artery and the brachial plexus were found to be stretched and compressed as they passed over an exostosis (? a cervical rib) of the first thoracic rib, the artery slightly distal to the exostosis having an aneurysmal dilatation The anomalous bone was removed with subsequent re appearance of the ipsilateral pulse and disappearance of the pain in the arm

During the last two years 3 cases of arterial compression in the thoracic outlet with complicating thrombosis have been diagnosed and treated at our hospital

Case reports

Case 1 Male aged 52 farmer was admitted because of a pulsating lump in the right supraclavicular fossa which he had first noticed one year previously During the previous month he had also developed numbness and weakness of the right hand with increasing pain in the fingers on the ulnar aspect On admission the right hand was atrophied and the muscles of the arm were weak The skin temperature began from a few centimetres below the shoulder joint to decrease distally There was no gangrene

Roentgen examination Cervical spine A rather large cervical rib was present on the right side

Angiography of the right subclavian artery A catheter was introduced into the femoral artery but could not be manipulated through the aortic arch into the innominate artery A catheter (PE 160) was therefore inserted into the right common carotid artery (Fig 2) and advanced



Fig 2 Case 1 a) Arteriography Catheter in right carotid artery Good filling of tortuous innominate artery common carotid artery and first part of subclavian artery Carotid artery manually compressed Large cervical rib on right side b) Subclavian artery occluded immediately distal to the origin of internal mammary and vertebral arteries Several collaterals especially from the widened internal mammary artery pass out into the arm

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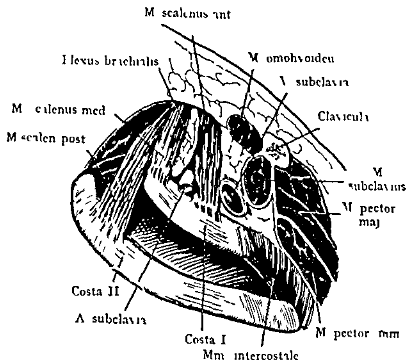


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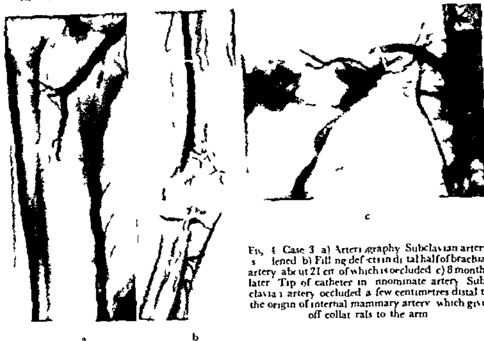


Fig. 4. Case 3. a) Arteriography. Subclavian artery s lened. b) Filling defects in distal half of brachial artery about 21 cm of which is occluded. c) 8 months later. Tip of catheter in innominate artery. Subclavian artery occluded a few centimetres distal to the origin of internal mammary artery which gives off collaterals to the arm.

Angiography of the right subclavian artery 8 months after the first examination (Fig. 4c). The lumen of the middle third of the vessel was occluded for a length of about 5.5 cm. The bulk of the contrast medium passed out into the arm through the collaterals via a widened internal mammary artery and the transverse cervical branch of the thyrocervical trunk. Some 9 cm of the axillary artery were filled via collaterals; the distal part of this artery showed multiple filling defects and was occluded.

Operation. The middle third of the clavicle was resected and the brachial plexus and subclavian artery and vein were dissected free from massive adhesions. The thrombus was removed from the subclavian artery and a satisfactory blood flow re-established.

The postoperative course was uneventful and the circulation and the muscle strength of the right arm improved.

Angiography of the right subclavian artery two months after operation (Fig. 5). The distal part of the subclavian artery was still patent and dilated at the former site of the thrombosis. Angiography was as at the first occasion repeated but with the arm hyperabducted (Fig. 6). The subclavian artery was occluded below the clavicle, as before the operation, and the contrast medium passed into the arm via the collaterals.

Operation. The scalenus anterior was divided.

The patient has felt well after the operation and the arm has almost completely recovered its original strength.

Discussion

Symptoms due to compression of the brachial plexus at the cervico-brachial junction are much more common than corresponding vascular symptoms and clearly predominate in women (Eden).



a b

Fig 3 Case 2 a) Tip of catheter in right subclavian artery innominate artery first part of subclavian artery and common carotid artery contrast filled Subclavian artery occluded immediately distal to the origin of internal mammary artery Collaterals to the arm b) Patent axillary and brachial arteries S shaped catheter with tip in subclavian artery well depicted

and vertebral arteries and the thyrocervical and costocervical trunks The axillary artery was supplied by collaterals from the internal mammary artery and the thyrocervical and costo cervical trunks The subclavian artery was thrombosed along some 5 cm of its length

Operation The cervico axillary canal was found to be narrow and to contain abundant fibrotic tissue The subclavian artery which had degenerated into a rigid cord contained an old thrombus The tendon of the scalenus anterior was divided and the nerves and the vessel were dissected

The patient felt better immediately after the operation but about one year later the vascular and nervous symptoms gradually returned

Case 3 Male aged 27 builder s labourer had for 4 weeks frequently had a tingling sensation in the right hand this was often followed by pain in the lower arm especially when carrying heavy loads on the shoulders with the hands over the head On admission the right hand was found to be cold and the fingers pale The right radial pulse was impalpable but pulsations of the brachial artery could be felt in the cubital fossa Treatment with a stellate block for one week produced some improvement

Roentgen examination The cervical spine was normal

Angiography of the right subclavian and brachial arteries by the same method as in Case 2 widening of the former vessel and small irregularities in the outline of its wall (Fig 4a) filling defects were present in the distal half of the brachial artery which was completely obliterated along 21 cm of its course (Fig 4b)

The patient was treated with anticoagulants and massage of the right hand Gangrene devel oped in the tips of digs II and III but was rather limited and healed after some small fragments of necrotic tissue had been shed Treatment was continued for 4 months The patient returned to work without any appreciable symptoms At control examination the skin temperature of the right arm and hand was about the same as on the left side There was no gangrene The right radial pulse was *impalpable*



Fig 6 Case 3 (same as in figs 4 and 5) a) Examination performed with the arm abducted as much as possible Subclavian artery occluded where it crosses the clavicle b) Axillary artery filled only through collateral and mostly from the internal mammary artery

thoracic scoliosis is quite common In scoliosis of this region the ribs on the convexity are elevated and may contribute to a compression syndrome

Various changes in the clavicle may also give rise to a compression syndrome e g a fracture with abundant callus an ununited fracture or a fracture joined in malposition (POKER et coll 1958)

Nerves As pointed out by JONES (1913) the contribution to the brachial plexus from different nerve roots varies with the rib anomalies The plexus is usually prefixed i e has a contribution from the fourth cervical root and only a small one from the first thoracic root when a cervical rib is present If however the plexus lacks the contribution from the fourth cervical root and receives a considerable contribution from the first thoracic root i e is postfixed the first thoracic rib is rudimentary The degree of prefixation thus varies with the completeness of the cervical rib When the cervical rib is short the nerve may be compressed but if it is a complete rib the brachial plexus arises from one segment higher up and will not be compressed The relations of the subclavian artery however are not subject to the same sort of variation as those of the nerves and will be more easily compressed by a complete cervical rib than by a small incomplete one (GLADSTONE & WAKELY 1932) This is probably the reason why vascular and nervous complications of cervical ribs often appear separately (ROSS 1959)

TODD was of the opinion that the pathologic changes of the arteries arose



Fig 5 Case 3 (same as in fig 4) a) Arteriography Thrombus in the subclavian artery has been removed This part of the artery was also aneurysmatically widened at previous examination b) Axillary artery occluded distally Only collaterals pass out into the arm

Vascular complications in the thoracic outlet, however, occur only slightly more often in women and are about equally common in each arm According to EDEN only one case has been described (by RUSSEL in 1907) in which both arms were affected ADSON (1947) was later unable to confirm the statement of EDEN that vascular complications are somewhat more common among manual workers Most patients have been young or middle aged although their ages have varied between 5 and 75 years

Anomalies favouring development of the syndrome

Bones The cervical rib is the most wellknown abnormality causing the thoracic outlet syndrome *It is often bilateral but may be unilateral without any* predilection for one side or the other The anomaly is more than twice as common in women as in men

The 1st thoracic rib is sometimes rudimentary (KEEN) and may then cause a compression syndrome in the same way as a cervical rib The rudimentary rib is about as common as the cervical rib but is usually unilateral (TODD 1912, HAVEN 1939, ETTER 1944, SYCAMORE 1944) The occasional articulation of the 1st thoracic rib is usually of development origin (WHITE et coll 1945) This articulation, as well as a fracture with abundant callus, may cause compression

Abnormal ribs are rarely the only skeletal abnormality present (WALSHE 1951), defects in the vertebral bodies and laminae, with consequent cervico



Fig 7 Normal appearances of subclavian artery when the arm is to the side (a) but completely compressed under clavicle when arm is abducted (b) Anterior scalenotomy produced no improvement in the appearances

otherwise healthy individuals POMMERENKE and RISTEEN (1944) pointed out that in some cases a scalenus anticus syndrome developed after prolonged gynaecologic operations in the Trendelenburg position with the head hyper extended and one of the arms abducted *for i v fluid* administration WRIGHT (1945) described a neurovascular syndrome produced by hyperabduction of the arm He studied *the effect of hyperabduction on the* radial pulse in 150 young men in one third of them the pulse was easily obliterated and after rather small adjustments in as many as 83 % *only in 17 %* was the pulse not affected He ascribed the compression to the *passage of the* artery under the pectoralis minor and coracoid process or between the clavicle and first rib The syndrome appeared after prolonged hyperabduction *during* sleep or work

According to STAMMERS (1950) Morissey in students studied the effect of various positions of the arm on the *radial pulse He* confirmed the results of TELFORD & MOTTERSHEAD and found that almost any muscular man can obliterate his radial pulse by active abduction of the arm against the trunk by the action of retraction (bracing *of the* shoulders) obliterates the pulse in over 60 % of normal men and women that active abduction with extension diminishes or obliterates the pulse in about 50 % of normal cases and that Adson s test was positive in many normal individuals

STEIN (1946) measured the *blood* pressure in the arm held in different positions he often found a lowering of the systolic pressure, though moderate when the arm was hyperabducted

from interference with certain sympathetic nerve fibres, but LEWIS and PICKERING (1934) considered the vessel changes to be purely of a mechanical nature

TELFORD and MOTTERSHEAD (1948) from postmortem investigations described a gripping effect of the median nerve heads around the axillary artery in forced depression of the shoulder This theory has apparently attracted but little attention by other investigators

Muscles Abnormalities of the bones in the thoracic outlet are usually associated with anomalies in the insertions of the scalene muscles In the presence of a cervical rib, the anterior and middle scalene muscles may have insertions into it as well as into the first thoracic rib Scalenus medius and posterior may have insertions into the cervical rib alone, or into this and the first and second thoracic rib, or there may be no insertions into a cervical rib In the case of rudimentary first rib, the scalenus anterior may have two or three slips of insertion into its posterior bony and intermediate fibrous portions

Both the subclavian artery and the nerve roots may also occasionally traverse the scalenus medius, dividing it into fasciculi A scalenus minimus may also be present, lying as a slip between the scalenus medius and anterior with insertions into the first rib and, in some instances, the dome of the pleura (see WALSHE)

The most important effect of the scalene muscles in this syndrome is that they probably prevent any forward downward sliding of the nerve trunks and the artery from the uppermost rib Reports of successful scalenotomy operations also point in this direction

Some authors have described hypertrophy of the scalene muscles, and others a spasm, the artery being compressed by the muscles The evidence is, however, according to STAMMERS, insufficient

The different more or less abnormal anatomic structures described are often not enough in themselves to cause the compression syndrome The age distribution with preponderance for middle aged women has been interpreted as depending upon the drooping of the shoulders in these patients The artery is then stretched over the abnormal bone more than early in life

ADSON pointed out that in the scalenus anterior syndrome the subclavian artery may be compressed still further by inspiring with the head tilted backwards and turned to the affected side

LEWIS and PICKERING observed in a case of a cervical rib that the clavicle and the cervical rib compressed the subclavian artery when the arm was abducted to 90° FALCONER and WEDDELL (1943) described a costo clavicular compression syndrome in soldiers carrying heavy packs, the artery being compressed between the clavicle and the uppermost rib, in the position of 'attention when the shoulders were braced, the radial pulse was occluded in one third of the



Fig 8 Non-opaque catheter was introduced into the first part of left subclavian artery but recoiled into aorta during injection Subclavian artery cone shaped and occluded at the origin of internal mammary artery which is narrow and most of the collaterals to the arm probably stem from intercostal arteries given off by the thoracic aorta

fundamental experiments in animals and showed that the poststenotic dilatation became greatest when the lumen of the artery was reduced to about one third or perhaps one fourth of its original size HOLMAN (1954) continued the work of HALSTED and also made experiments with a circulatory model with a pulsating flow which showed the mechanism of the poststenotic dilatation The velocity of flow increases at a constriction and when this rapidly ejected stream strikes the more slowly flowing distal stream high kinetic energy is suddenly converted into high potential energy or lateral pressure The poststenotic turbulent eddies strike the walls of the vessel with alternating high and low pressure waves which can be palpated as a thrill After some time the oscillations in pressure result in structural fatigue giving a poststenotic dilatation of the vessel

A thrombus may now and then be formed in the poststenotic dilatation by the blood platelets being damaged by the turbulent eddies this may in turn produce emboli in the arm and cause the same symptoms as mentioned

Roentgen diagnosis

The roentgenologic investigation is first directed towards the skeleton in the thoracic outlet with special regard to various anomalies and to fractures

Angiography is however necessary for a correct and detailed diagnosis ÖDMAN (1956) briefly mentioned a case of calenus anticus syndrome with cervical ribs The figures show a bilateral narrowing of the subclavian arteries but no other vessel changes We generally use Ödman s method with a straight catheter for the left subclavian artery and an S-shaped catheter for the right subclavian

We have performed subclavian arteriography in 17 cases (Cases 1, 2 and 3 not included) with the arm at the side as well as abducted as much as the patient could stand for some minutes, i e usually not an extraordinarily exaggerated position In a case diagnosed clinically as a scalenus anterior syndrome of arterial type there was, on abduction of the arm, nearly complete compression of the subclavian artery at the site where it passed under the clavicle, and collaterals were seen Anterior scalenotomy was performed but at subsequent angiography no improvement was evident (Fig 7) In 5 cases there was only a slight narrowing of the subclavian artery with no evidence of collaterals on abduction of the arm In 11 cases the artery was not compressed at all on abduction A narrowing of the subclavian artery in a purely mechanical way can thus be achieved when the arm is held in an unnatural position or in the presence of anatomical abnormalities in the thoracic outlet Thus it seems unnecessary to resort to more or less elaborate theories about any mechanism interfering with the sympathetic nerves, spasm of the muscles caused by nerve compression, and so on The reason why the compression syndrome is fairly uncommon is that the exaggerated positions of the arm, often necessary for compressing the artery, are usually not maintained for any longer period of time

Complications caused by compression of the subclavian artery

A pure compression of the subclavian artery will give only slight ischaemia of the arm as a rich collateral system is easily established Fibrosis, causing permanent narrowing of the structures passing through the thoracic outlet, will sometimes be produced by small, repeated traumata due to ordinary movements of the arm, neck, diaphragm, and increase the compression of the artery (Case 2) If a thrombosis develops it may occlude some of the collaterals and increase the symptoms and make them permanent (Case 1) Only if embolies are thrown off out into the arm and block arteries more peripherally will the ischaemia be intense (Case 3) Gangrene is often localized only to one finger tip, usually the index finger, even if the block is in the brachial artery and the more peripheral vessels are patent

Occasionally, though rarely, a thrombus in the right subclavian artery has grown in a proximal direction and occluded the right carotid artery A block of the inferior part of the vertebral artery will usually give no symptoms as the other cerebral arteries, if normal, will be sufficient for the blood supply to the brain If, however, the carotid artery is occluded or if emboli are thrown up into the cerebral arteries, hemiplegia or similar serious neurologic complications may result (see HOOBLER 1942) On account of the vascular anatomy a corresponding phenomenon on the left side has never been described

The subclavian artery is sometimes dilated fusiformly just distal to the narrowing in the thoracic outlet This aneurysmal dilatation has received much attention and many theories have been propounded HALSTED (1916) made

vestigation of the subclavian arteries The quantity of contrast medium given must be large however and nevertheless the concentration of the contrast medium in the subclavian arteries will be low for these reasons the method has never been used at Lund

Retrograde catheterization of the subclavian artery from the brachial artery, sometimes used by us in other cases should not be used in cases of impaired circulation of the arm and is also often impossible owing to occlusion of the vessel

It is necessary to pay due regard to the position of the arm in performing subclavian arteriography After serial angiography with the arm lying relaxed at the side of body it is often advisable to complete the examination with a new series with the arm in another position e g hyperabducted or with the patient in the sitting position with the arm loaded The history and the clinical examination will reveal the position most likely to provoke arterial compression

Differential diagnosis Thrombosis of the subclavian artery in the thoracic outlet may of course also be caused by conditions other than a compression syndrome e g atheromatosis syphilis and brachiocephalic arteritis These will usually lead to wide spread vessel changes In brachiocephalic arteritis the subclavian arteries are often conically narrowed (WICKBOM 1957) and the collaterals mostly developed from the thoracic aorta via the intercostal arteries and not often from the internal mammary artery or the thyreocervical and costocervical trunks which themselves have a diminished flow (Fig 8)

Radiotherapy for carcinoma of the breast may produce narrowing of a fair length of the vessel and sometimes thrombosis of the subclavian and axillary artery but the vessel changes and the location are quite different from those of the compression syndrome (Fig 9)

Slight narrowing of the subclavian artery occurring when the arm is placed in an unnatural position is of no diagnostic or clinical significance If however complete obstruction appears and collaterals are seen a compression syndrome may be regarded as present and complications may develop if the position is maintained for any length of time

An arterial embolus can of course impair the blood supply to the arm but the embolus is thrown off from some pathologic part of the cardiovascular system which may then be found Acute ischaemia of the arm in a case of an embolus cannot be used as a differential diagnostic sign as the first evidence of a compression syndrome may be a brachial embolus (Case 3)

Angiography as well as a thorough study of the subclavian artery in different positions of the arm during operation should clarify the position of the vessel in relation to its surroundings and indicate whether extirpation of some of the bony parts in the thoracic outlet is necessary Supplementary vascular surgery such as thrombectomy and sympathectomy is sometimes advisable



a b



c

Fig 9 Case of operated and irradiated carcinoma of the right breast 14 years previously no recurrence The muscles of the right arm were weaker and the skin temperature was lower on that side Irregularly narrowed subclavian artery with axillary artery occluded for a few centimetres Internal mammary artery also irregularly narrowed and no larger collaterals given off The vessel changes were probably due to previous irradiation

artery, in adults we employ a PE 205 catheter In elderly patients the catheterization may be difficult, especially on the right side In such cases the common carotid artery is punctured and a thin polythene catheter (*PE 160*) introduced against the blood stream down into the innominate artery (Case 1) To prevent too much contrast medium entering the brain circulation, the carotid artery is compressed during its injection (SELDINGER 1957)

Angiography by direct puncture of the subclavian artery was used by CRAWFORD et coll (1959) but caused a pneumothorax in 20 % of the cases and has not been practised by us Thoracic aortography has been employed by WICKBOM (1957) and others in cases with impaired blood flow through the subclavian arteries, he placed the tip of the catheter as near the origin of the desired vessel as possible in order to obtain as good a filling as possible of the brachiocephalic arteries Selective injection directly into the desired vessel however is of course, preferable STEINBERG (1957) and others used angiocardiography in the in

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SUMMARY

The arterial complications in thoracic outlet compression syndrome is discussed Three cases are presented The angiographic technique is mentioned and the diagnostic value of selective subclavian angiography is stressed Valuable information may be obtained by serial angiography with the arm in various positions

ZUSAMMENFASSUNG

Die arteriellen Komplikationen im "thoracic outlet compression syndrome" werden in Kurze studiert Es werden drei Falle prasentiert Die angiographische Technik wird erwahnt und der diagnostische Wert der selektiven Subclavia Angiographie hervorgehoben Wertvolle Information kann durch Serienangiographie mit dem Arm in verschiedenen Positionen er halten werden

RÉSUMÉ

L auteur décrit brièvement les complications artérielles du thoracic outlet compression syndrome Il en présente trois cas Il décrit la technique angiographique et souligne l intérêt de l angiographie sous claviere sélective L angiographie en serie dans différentes positions du bras donne des renseignements de valeur

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ROM THE DEPARTMENT OF WOMEN'S DISEASES (DIRECTOR LATE PROF AXEL
ESTMAN) AND THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF KNUT
LINDBLOM) KAROLINSKA SJUKHUSET, STOCKHOLM SWEDEN

HYDATIDIFORM MOLE DIAGNOSED BY PELVIC ANGIOGRAPHY

by

ULF BORELL and INGMAR FERNSTRÖM

The value of pelvic angiography in the diagnosis of hydatidiform mole and choriocarcinoma was the subject of previous papers (BORELL FERNSTRÖM & WESTMAN 1955 1958) and the details of the technique of this method of examination were described by FERNSTRÖM (1955) At that time it had not previously been possible to describe in detail the angiographic appearances associated with hydatidiform mole because only one case had been examined by pelvic angiography and the major part of the tumour had then been removed prior to the examination

Hydatidiform mole has subsequently been diagnosed by pelvic angiography in a further 5 cases A careful review of the angiograms confirmed the diagnostic value of this method of examination and revealed certain characteristic appearances

Clinical features The relevant features of the 5 case histories are summarized in the Table on p 114

All the patients were nulliparous and their ages varied between 23 and 29 years

In most cases the initial sign was vaginal haemorrhage or a blood stained vaginal discharge, first evident towards the end of the third month of preg

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Table

Relevant features of the case histories

Case No	Age	Previous pregnancies	Time of appearance of initial signs*	Size of uterus at time of roentgen examination	Time of roentgen examination*	Time of delivery*	Delivery	Histological diagnosis
1	29	0	12	Abnormally enlarged	14	22	Vaginal evacuation	Hydatidiform mole
2	23	0	8	Abnormally enlarged	15	16	Abdominal hysterotomy	»
3	2[illegible]	1 miscarriage	10	Consistent with the duration of pregnancy	19	23	Spontaneous	Not available
4	25	0	13	Abnormally enlarged	17	18	Vaginal evacuation	Hydatidiform mole
5	24	0	12	Abnormally enlarged	13	14	Abdominal hysterotomy	»

* Maturity in weeks

nancy With the exception of one case in which the size of the uterus corresponded to the duration of the pregnancy, clinical examination revealed abnormal enlargement of the uterus

The patients were examined roentgenologically between the thirteenth and nineteenth weeks of pregnancy For purposes of comparison the angiograms of 30 patients who had been examined between the third and fifth months of a normal pregnancy, were reviewed All these last patients later underwent therapeutic abortion

Roentgen appearances

A survey film of the abdomen was taken with the patient supine and the over couch tube In order to provide favourable conditions for the demonstration of the foetal skeletal parts, care was taken to avoid superimposition of the maternal bony tissues on the uterus The tube was therefore angled 15 to 20° caudally However, in no case was a foetal skeleton identified

The angiographic appearances differed from those associated with a normal pregnancy, with the exception of one case the intervillous spaces were seen to be fewer in number and more widely separated as compared with those in normal cases

The contours of the intervillous spaces were also characteristic, being in some places smoothly curved (Figs 1, 2, 5)



Fig 1 Hydatid form mole (Case 2) Four seconds after end of inject on of contrast med um The intervillous spaces are clearly v sible they are sparse and some have smoothly curved contours (arrows)



Fig 2 Hydat d form mole (Case 3) Fo r seconds after end of inject on of con trast med m A la ge number of ntervillous spaces some of which have smooth ly curved contours (arrows)

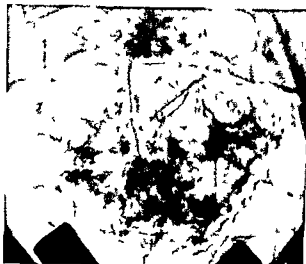


Fig 3 Normal intra uterine pregnancy at 4th month Four seconds after end of injection of medium numerous intervillous spaces lying closely together and with irregular and frayed contours



Fig 4 Missed abortion at 4th month of pregnancy Four seconds after end of injection of medium the intervillous spaces are seen in the form of irregular opacities that are not frayed

The tumour was removed either by abdominal hysterotomy or by vaginal evacuation The clinical and roentgen diagnoses of hydatidiform mole were confirmed by histologic examination in all but one case (Case 3) In this latter case the concentration of chorionic gonadotrophin in the urine was determined immediately after pelvic angiography and was found to be markedly increased This also strongly suggested the presence of a hydatidiform mole Four weeks later the patient, then abroad, was delivered spontaneously and, according to information given by letter, produced a mole Histologic examination of the tumour was not carried out

Discussion

The clinical diagnosis of hydatidiform mole may be difficult, the only reliable diagnostic sign being the presence of vesicles in the vaginal discharge However, this may be a comparatively late manifestation and before the expulsion of vesicles only a tentative clinical diagnosis can be made, usually based on excessive enlargement of the uterus associated with a watery and blood stained vaginal discharge The concentration of chorionic gonadotrophin may be a guide to the diagnosis

Roentgen examination of the abdomen and bony pelvis may often be of considerable value in this condition The absence of the foetal skeleton in the survey *films is a suggestive feature But as the foetal skeleton is rarely* sufficiently calcified to be visible in films taken prior to the sixteenth week of pregnancy a survey film of the maternal abdomen at that time will be of little



Fig 5 Schematic representation of intervillous spaces in normal pregnancy (middle) hydatidiform mole (left) and missed abortion (right)

value in the diagnosis The absence of foetal parts led to the correct conclusions in the two patients of the present series who were examined roentgenologically after the sixteenth week of pregnancy

Pelvic angiography enables the diagnosis of hydatidiform mole to be made irrespective of the duration of pregnancy because the appearances are already characteristic at a very early stage of gestation the outstanding features being smoothly curved contours of *some of the intervillous spaces* (Figs 1 2 and 5, left sketch) the stroma of the villi undergoes cystic degeneration which results in the formation of vesicles that vary in size from 1 mm to more than 1 cm and account for the smoothly curved contours of the intervillous spaces Demonstration of only a small number of intervillous spaces is a further guide to the diagnosis It is possible that the majority of the intervillous spaces are not outlined because they are filled with vesicles

In all the cases of the control group a large number of intervillous spaces with irregular and frayed contours were visible (Figs 3 5, middle sketch) In certain circumstances such as missed abortion the villi undergo necrosis, the intervillous spaces being thereby enlarged The latter are then demonstrated as relatively large opacities with irregular contours but not frayed (Figs 4 and 5 left)

A study of the angiographic appearances of the *intervillous spaces thus* makes it possible to differentiate between normal and oedematous or necrotic villi

Pelvic angiography has also been found to be helpful in the diagnosis of mole destruens and choriocarcinoma (BORELL et coll 1955 1958) This method of examination may prove to be of particular value in cases of *intramural* choriocarcinoma which are difficult to diagnose clinically Characteristic features of the angiogram are hypervascularity of the uterus particularly at the site of the tumour and irregularly outlined *cavities* as well as arteriovenous fistulae within the area of the tumour The angiographic appearances of mole destruens and choriocarcinoma therefore differ greatly from those associated with *hydatidiform mole* This enables the differential diagnosis between these conditions to be made

The diagnosis of hydatidiform mole would probably be difficult if only a minor degree of cystic degeneration were present because the changes in the villi would be too small to be demonstrated. In such cases the appearances could easily be confused with those associated with a normal pregnancy. For this reason it is advisable to keep the patient under careful observation and to perform further pelvic angiography a few weeks later if the presence of hydatidiform mole is still indicated.

SUMMARY

Pelvic angiography confirmed the clinical diagnosis of hydatidiform mole in 5 cases. Intervillous spaces with occasional smoothly curved contours were a characteristic feature of the condition. The differential diagnosis is discussed.

ZUSAMMENFASSUNG

Eine Beckenangiographie bestätigte in 5 Fällen die klinische Diagnose einer Blasenmole. Die intervillösen Räume mit gelegentlich sanft gekrümmten Konturen waren ein für diese Erkrankung charakteristisches Bild. Die Differentialdiagnostik wird besprochen.

RÉSUMÉ

L'angiographie pelvienne a confirmé le diagnostic clinique de mole hydatiforme dans 5 cas. Les signes caractéristiques de cette affection sont les espaces intervilleux limités par endroits par des contours courbes réguliers. Le diagnostic différentiel est étudié.

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF SOLVE WELIN)
MALMO ALLMANNA SJUKHUS SWEDEN

VARIATION IN SIZE OF SPLEEN INDUCED BY WATER LOAD AS DIAGNOSTIC TEST OF JAUNDICE

by

TORSTEN ALMEN and LARS ANDREN

ANDRÉN (1957) described a splenic reaction test based on the measurement of the organ before and after the ingestion of a relatively large amount of fluid The normal spleen was found to increase 1 to 2 cm in length on the ingestion of one litre of water the enlargement disappearing within an hour in certain diseases including hepatitis no such enlargement was demonstrable This prompted the present investigation of the effect of a water load on the size of the spleen in a large series of cases of jaundice

Method The patients were examined in the prone position with the beam vertical (FFD 1 5 m) One film was obtained before the ingestion of the water two or three films at short intervals following it and one film 60 minutes later Immediately prior to the exposure of each film the patient was given a little soda water in order to ensure that gas was present in the fornix of the stomach with the fornix filled with gas the outline of the upper pole of the spleen is easier to define

Material The material consisted of 13 cases of obstructive jaundice and 46 cases of hepatocellular jaundice

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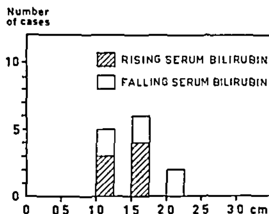


Fig. 1. Increase in length of spleen by water load in 13 cases of obstructive jaundice.

All the patients with obstructive jaundice had a raised serum alkaline phosphatase, and one of the following surgically verified conditions: (1) stone in the common bile duct, (2) stricture of the common bile duct with dilatation of the ducts above the stricture, (3) stone in the gallbladder + dilated common bile duct + biliary stasis and (4) cholecystitis + cholangitis + a dilated common bile duct containing thick bile.

Of the 46 cases of hepatocellular jaundice the condition was due to epidemic hepatitis in 43, to inoculation hepatitis in 2 and to drug (Marsilid) poisoning in 1. The diagnosis of epidemic hepatitis was based on a known exposure to an epidemic, to clinical features, to a raised serum transaminase or other signs of hepatocellular damage, and in 2 cases on liver biopsy.

The spleen increased in length by at least 1 cm in all the 13 cases of obstructive jaundice following the ingestion of the water, seven of the cases being examined while the serum bilirubin was rising and six while it was falling (Fig. 1). The length of the spleen averaged 13 cm (range 10 to 16 cm).

Thirteen of the 46 cases of hepatocellular jaundice were examined while the serum bilirubin was rising, and in 10 the length of the spleen remained unaltered, or increased at the most by 0.5 cm and in 1 case by 1 cm (Fig. 2); in these cases the length of the spleen averaged 16 cm (range 12 to 23 cm). The remaining 33 cases were examined while the serum bilirubin level was returning to normal; in 8 the spleen increased in length by less than 0.5 cm, in 7 by less than 1 cm, while in 18 cases the spleen reacted in a normal way, i.e. it increased by more than 1 cm. The length of the spleen before the test in these 33 cases averaged 14 cm (range 10 to 18 cm).

Seventeen of the cases of hepatitis were examined on two occasions at an interval of 1 to 12 weeks. Fifteen patients recovered from their jaundice and in all of them the spleen was smaller on the second occasion; in 11 of them the spleen reacted more markedly to the second test. In 2 patients the spleen was larger on the second occasion and reacted less strongly to the test. Both of these had a recurrence and one died in hepatic coma.

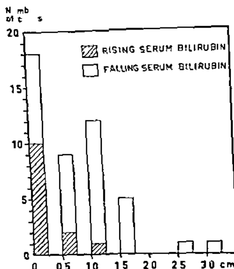


Fig ? Increase n length of spleen by water load in 46 cases of hepatocellular jaund ce.

Results

All of the cases of obstructive jaundice reacted to the test in a normal way, i e an increase of more than 1 cm in the length of the spleen Two cases were subjected to surgical exploration for probable obstructive jaundice In neither of them was the water load followed by any increase in length of spleen and the test was thus against obstructive jaundice In both cases the bile ducts were of normal appearance and liver biopsy showed liver necrosis Of the 13 cases of hepatocellular jaundice examined while the serum bilirubin was rising only one reacted in a normal fashion to the water load, while in all the cases of obstructive jaundice the water load was immediately followed by elongation of the spleen by 1 cm or more

In the cases of obstructive jaundice the average length of the spleen was not so great as in the cases of early hepatitis (13 cm against 16 cm) In the cases of hepatitis which healed and which were examined twice the length of the spleen was less and the organ reacted more markedly to the water load on the second occasion than on the first

Discussion

ANDRÉN (1937) offered the following tentative explanation for the reaction of the spleen to the water load The ingestion of such a relatively large amount of water may increase the flow of the blood through the portal system and thereby the portal pressure This possibility is supported by the finding that

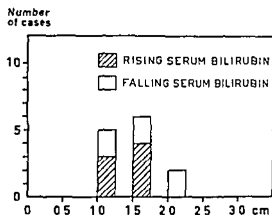


Fig 1 Increase in length of spleen by water load in 13 cases of obstructive jaundice

All the patients with obstructive jaundice had a raised serum alkaline phosphatase, and one of the following surgically verified conditions (1) stone in the common bile duct, (2) stricture of the common bile duct with dilatation of the ducts above the stricture, (3) stone in the gallbladder + dilated common bile duct + biliary stasis and (4) cholecystitis + cholangitis + a dilated common bile duct containing thick bile

Of the 16 cases of hepatocellular jaundice the condition was due to epidemic hepatitis in 13, to inoculation hepatitis in 2 and to drug (Marsilid) poisoning in 1 The diagnosis of epidemic hepatitis was based on a known exposure to an epidemic, to clinical features, to a raised serum transaminase or other signs of hepatocellular damage, and in 2 cases on liver biopsy

The spleen increased in length by at least 1 cm in all the 13 cases of obstructive jaundice following the ingestion of the water, seven of the cases being examined while the serum bilirubin was rising and six while it was falling (Fig 1) The length of the spleen averaged 13 cm (range 10 to 16 cm)

Thirteen of the 46 cases of hepatocellular jaundice were examined while the serum bilirubin was rising, and in 10 the length of the spleen remained unaltered, or increased at the most by 0 5 cm and in 1 case by 1 cm (Fig 2), in these cases the length of the spleen averaged 16 cm (range 12 to 23 cm) The remaining 33 cases were examined while the serum bilirubin level was returning to normal, in 8 the spleen increased in length by less than 0 5 cm, in 7 by less than 1 cm, while in 18 cases the spleen reacted in a normal way i e it increased by more than 1 cm The length of the spleen before the test in these 33 cases averaged 14 cm (range 10 to 18 cm)

Seventeen of the cases of hepatitis were examined on two occasions at an interval of 1 to 12 weeks Fifteen patients recovered from their jaundice and in all of them the spleen was smaller on the second occasion, in 11 of them the spleen reacted more markedly to the second test In 2 patients the spleen was larger on the second occasion and reacted less strongly to the test Both of these had a recurrence and one died in hepatic coma

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the enlargement diminished considerably or disappeared as soon as the subject assumed the erect posture The decrease in size on change of posture is probably due to a decrease in hydrostatic pressure in the splenic vein' ATKINSON & SHERLOCK (1954) and DAVIS et coll (1954) showed that the intrasplenic pulp pressure closely reflects the portal pressure

REICHMAN and DAVIS (1957) stated that the intrasplenic pressure as measured by puncture is increased in the acute phase of hepatitis but is on the average one third lower during convalescence

The increase in the portal pressure may be responsible for splenomegaly in the early stage of hepatitis, an increased tension of the capsule of the spleen preventing the normal reaction of the spleen to an increased flow of blood through the vena porta On regression of the hepatitis, portal stasis regresses, the enlargement of the spleen decreases, and the spleen is then again able to react in a normal way to variations in the portal pressure induced by the water load

ARONSEN and NYLANDER (1960) have shown in dogs that contrast medium injected for lienoportal venography passes through the liver quicker when the common bile duct is ligated suggesting that such ligation does not produce portal stasis This fits in well with our observations that in human subjects with obstructive jaundice the spleen reacted in a normal way to the water load

The investigation provides support for the assumption that the changes in the size of the spleen following the ingestion of a relatively large amount of water are due to changes in the portal pressure

The water load test is thus a useful tool in the differential diagnosis of jaundice, and is of value in following the course of hepatitis The spleen is enlarged in the acute phase of hepatitis

SUMMARY

Application of the water load test of the spleen in a series of 59 cases of obstructive and hepatocellular jaundice proved that the test is reliable in the differentiation between these two types of jaundice and that the spleen is enlarged in the acute phase of hepatitis

ZUSAMMENFASSUNG

Anwendung der Wasserbelastungsprobe der Milz hat sich in einer Serie von 59 Fallen von obstruktiver und hepatozellularer Gelbsucht in der Differenzierung dieser zwei Gelbsuchtstypen als zuverlasslich erwiesen und ergeben dass die Milz in der akuten Phase der Hepatitis vergrossert ist

RÉSUMÉ

L application de l épreuve de surcharge hydrique de la rate dans une série de 59 cas d ictère par rétention et par hépatite a montré que cette épreuve est fidèle pour différencier ces deux types d ictère et que la rate est augmentée de volume à la phase aigue de l hépatite

tissue in the ova and follicles This paper deals with the investigations of the antineoplastic effect of lithium both in animals and clinical experiments

Animal experiments The action of lithium was studied in a lymphatic leukaemic tumour, NJ in AKA mice and in an adenocarcinoma PBH, in C_3H mice Both these tumours are homologous since they have arisen and been retransplanted in the respective inbred mouse strains The transplantation of the tumours was performed by the subcutaneous injection of approx 10^6 tumour cells into the right axilla all injections resulting in takes Lithium was given by daily intraperitoneal injections of LiCl prepared from the stable Li_2CO_3 the control animals were given similar injections of NaCl In the experiments with the lymphatic tumour NJ lithium was administered in doses of 2 5 mEq/kg and 5 0 mEq/kg daily

The low dose given from the first day after transplantation, had no influence on the survival time of the animals which like the control animals died in from 11 to 13 days When the dose was increased to 5 mEq/kg daily given from the fourth day after transplantation the treated animals died before the controls Uninoculated AKA mice tolerated 5 mEq/kg daily for more than 20 days without the development of any toxic symptoms In similar experiments with the adenocarcinoma PBH even the low dose of 2 5 mEq/kg daily killed the treated animals in about 20 days while the controls lived for about 28 days in toxicity experiments on uninoculated animals this dose was tolerated for more than 40 days The high dose of 5 mEq/kg daily that was commenced later in the experiment likewise exerted only a toxic effect and killed the animals in about 16 days after the transplantation All animals which succumbed were studied histologically but no changes in the composition of the tumour, metastases or leukaemic infiltrations into the organs of the animals were demonstrated

The tumour size was followed in both series of experiments In the experiments with NJ leukaemia no difference in the size of the tumours in the treated animals and the controls could be demonstrated but in those with the PBH adenocarcinoma the tumours grew more slowly in the treated than in the control animals However as the former lost weight more rapidly than the latter no significance can be attributed to the lower tumour growth rate in the treated animals in the evaluation of the effect of lithium since a certain relationship exists between the nutritional state of the animals and the tumour growth

Further experiments were performed with the tumour types tabulated below

Designation	Type of tumour	Mouse strain
JBI	Reticulosarcoma	C_3H
Krebs II	Anaplastic carcinoma	AKA
GH	Adenocarcinoma	Street
Ehrlich	Carcinoma	C_3H

FROM THE INSTITUTE OF GENERAL PATHOLOGY (DIRECTOR J. BICHEL), UNIVERSITY OF AARHUS, AND THE RADIUM CENTRE FOR JUTLAND (DIRECTOR C. KREBS), AARHUS, DENMARK

EXPERIMENTS WITH LITHIUM IN CHEMOTHERAPY OF CANCER

by

JØRGEN HASTRUP

A constantly increasing number of patients in the manic phase of manic depressive psychosis have been treated with lithium during the last 10 years. Professor F. H. Shaw, the pharmacologist of Melbourne, visited the Institute of General Pathology in 1958. He mentioned that an antineoplastic effect of *lithium had been observed in patients with manic* depressive *psychosis who* also suffered from cancer and suggested that these observations might be investigated.

It has repeatedly been shown that lithium is capable of inducing a growth change *in* embryonic tissue, e. g. sea urchin eggs, resulting *in developmental* anomalies. In addition, lithium interferes with metabolic processes in various tissues through a change in the catalysis of reactions in which energy rich bonds change places. (For a survey of the pharmacologic and biologic prop*erties of lithium the reader is referred to* SCHOU *1957.*)

According to CHEVREMONT COMHAIRE 1953, lithium is able to change the growth curves for chick fibroblasts and myoblasts in tissue culture and gives rise to a prolonged metaphase and the development of cells with abnormal nuclei. TRAUTNER et coll. *showed that the administration of lithium* reduces the number of corpora lutea in pregnant rats, and interpreted this observation as a result of a growth inhibiting effect of lithium on the rapidly proliferating

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Ten days later Li_2CO treatment was resumed with 300 mg daily but as mental dullness polyuria and excessive thirst accompanied by a coarse tremor and muscular fasciculations developed after about 10 days the treatment was discontinued During the latter period of treatment the serum Li was at a maximum of 0 56 mEq/l

Slight symptoms of lithium intoxication developed in several other patients in spite of small doses and a relatively low serum Li level

Three patients had certain peculiar hallucinatory experiences during the lithium treatment A 34 year old man with lymphosarcomatosis stated at a time when his serum Li occupied a level of from 1 10 to 1 50 mEq/l that he had a feeling as though he were lying on his left side in the bed although from his position in relation to the room, he realised that he was acutally lying on his right side He also thought he had seen someone (the author) get up from a chair at the bedside and walk round the bed back to the chair he afterwards realised that these observations were not founded upon objective reality He had similar fleeting impressions during the following two days Two other male patients aged 44 and 61 both suffering from myelomatosis had hallucinations which had certain features in common, during a course of lithium therapy given in the out patient department They thought they had seen and spoken to people both known and unknown who had appeared in their homes in the evening or at night One of the patients even went so far as to send the visitors away and lock the front door behind them These experiences seem to have occurred in the dark and it is very difficult to distinguish between them and dreams

It may be concluded from these few clinical experiments that lithium has no therapeutic effect on the disorders concerned Specific changes in the blood were not demonstrated The side reactions may perhaps be partially ascribed to the relatively poor general condition of the patients similar violent reactions to lithium therapy have not been observed in the State Mental Hospital at Aarhus where a large number of manic patients have been treated with lithium

It is difficult to assess the hallucinatory experiences of the three patients, it is beyond dispute that they occurred during lithium treatment and disappeared when this treatment was discontinued One of the patients was subjected to a psychiatric examination by Dr Stromgren who concluded that the experiences seemed to be of a hypnagogic origin the possibility that the lithium may have been a contributory factor in their development cannot however be excluded No reports on observations of similar hallucinatory experiences are available in the literature but BLEULER of Zurich has recently informed us that he had observed genuine hallucinations in one patient during lithium therapy Die Patientin halluziniert lebhaft Mucken optisch und mit dem Hautsinn

Lithium given in daily doses of 3 mEq/kg, however, did not prolong the survival time of the mice or inhibit the tumour growth in these experiments

It appears from these data that lithium exerted no antineoplastic effect on the mouse tumours studied It is worth noting that the tumour bearing animals did not tolerate lithium so well as similar healthy animals SIMON, TRAUTNER and COATS have recently reported an experiment in which they found that mice with an Ehrlich ascitic tumour retained larger amounts of lithium than the control animals, both after subcutaneous and oral administration In the present experiments, no Li analyses were carried out on the tumour bearing animals Serum analyses (performed in the Biochemical Laboratory of the State Mental Hospital, Aarhus) during the toxicity experiments gave results similar to those obtained by SCHOU after treatment of rats with toxic doses of lithium These animals died from renal damage (upper nephron nephrosis)

Clinical experiments A small group of patients with malignant disorders, as given below, were treated with lithium, during which period they received no other form of specific therapy

Malignant disorder	No of patients
Myelomatosis	4
Hodgkin s disease	4
Lymphosarcoma	2
Carcinoma of the breast	1
Carcinoma of the kidney	1
Mycosis fungoides	1

None of these cases revealed a favourable effect which could reasonably be ascribed to lithium, on the other hand, certain side reactions were observed

Manic patients are usually given an initial dose of 1 800 mg Li_2CO_3 daily, followed by a maintenance dose of 600 to 900 mg daily It soon appeared that patients with malignant disorders were unable to tolerate these high doses This is illustrated by the following brief case history

A woman aged 25 had suffered from Hodgkin s disease since 1955 and had been treated with several courses of roentgen irradiation d l diepoxybutane T E M and phenylbutazone On admission on 10 October 1958 she was acutely ill with high fever she had an enlarged spleen and was troubled by itching of the skin and nausea Haemoglobin (after three trans fusions) 62 % creatinine clearance 88 ml/min weight 60 kg The patient showed marked intolerance to alcohol (BICHEL) On 27 28 and 29 October she was given Li_2CO_3 300 mg × 4 The next day the patient complained of a feeling of weakness in the limbs accompanied by tremor of the hands Serum Li was determined as 2 47 mEq/l (a value exceeding 2 0 mEq/l may be toxic) accordingly the dose was reduced to 300 mg × 2 On 31 October only 300 mg Li_2CO_3 were given but confusion marked tremor and sopor developed gradually fading into coma The patient was still unconscious the following day although the serum Li after parenteral fluid therapy chiefly with NaCl had fallen to 1 28 mEq/l On 2 November the serum Li had fallen to 1 00 mEq/l and the patient was awake and could drink water unaided During the next few days her condition improved and on 5 November she responded rationally to questions although her speech was still slow and slurred The serum Li was now 0 23 mEq/l

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Acknowledgement

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SUMMARY

The treatment with lithium of malignant homologous mouse tumours and of 13 patients with malignant disorders produced no antineoplastic effects A diminished tolerance to lithium was observed both in the tumour bearing mice and in the patients

ZUSAMMENFASSUNG

Die Lithiumbehandlung von bösartigen homologen Mausetumoren und von 13 Patienten mit malignen Storungen erzeugte keine antineoplastische Wirkung Eine Herabsetzung der Lithiumtoleranz wurde sowohl bei den tumortragenden Mausen als auch bei den Patienten beobachtet

RÉSUMÉ

Le traitement par le lithium de tumeurs malignes homologues chez des souris et d affections malignes chez 13 malades n a eu aucun effet antinéoplasique On a constaté une diminution de la tolérance au lithium chez les souris porteuses de tumeurs et chez les malades

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FROM THE DEPARTMENT OF RADIATION THERAPY (DIRECTOR WALTER T MURPHY) AND THE DEPARTMENT OF STATISTICS (DIRECTOR IRWIN D J BROSS), ROSWELL PARK MEMORIAL INSTITUTE, BUFFALO NEW YORK U S A

EVALUATION OF THE PLACEBO EFFECT IN THE TREATMENT OF RADIATION SICKNESS

by

JOHN A PARSONS JOHN H WEBSTER and J E DOWD

In a recent study made in the Department of Radiation Therapy of this Institute it was found that 61 to 72 % of all patients suffering from so called radiation sickness would respond favorably to placebo medication A few years ago the drug literature was suddenly flooded by an increasing number of drugs of purported value in the treatment of radiation sickness Although this syndrome had never been considered a problem in this department it was felt that an evaluation of the comparative effectiveness of these drugs might be desirable Another important factor to be considered was the variable cost of these drugs Prior to this the drug of choice in the treatment of patients developing radiation sickness was pyridoxine This drug although maintaining a degree of popularity in many centers (MAXFIELD 1943 and SHORVAN 1949), has proven rather costly to the patients

A double blind study was therefore designed to compare eight different drugs each purported to be equally effective in the treatment of radiation sickness but before proceeding with the study it was deemed necessary to explore certain aspects of methodology and to evaluate certain variables of possible consequence to the determination of drug effects

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The patients were grouped according to whether they were receiving radiation below or above the diaphragm. No attempt was made to classify the patients according to the size of the field irradiated or the daily dosage. This would divide the patients into groups too small to study; the influence of these factors could be evaluated at the conclusion of the study.

A variable of possible equal importance might be the day of the week on which a patient first experienced symptoms; as patients treated in this department receive radiation therapy Monday through Friday, the day of onset of symptoms might thus provide a rough index of the amount of exposure to irradiation after a period of rest (i.e. the week end). The total radiation dosage, prior to experiencing symptoms, may also conceivably contribute to symptom severity.

The probable existence of a large proportion of placebo reactors in the treatment and control groups among patients reporting symptoms of radiation sickness would reduce observed differences and obscure real effects. This influence could be obviated by excluding placebo reactors, or it could be eliminated by numerical adjustment. Exclusion depends upon the use of a screening procedure, and a variety of specific procedures are possible. Numerical adjustment depends on having a reliable estimate of the proportion of placebo reactors, but the existing literature does not provide such an estimate. It was therefore decided to set up a methodologic study preliminary to the systematic evaluation of drug effectiveness in relieving symptoms of radiation sickness. It was decided to employ a known anti-emetic (prochlorperazine SKF, kindly supplied as 'Compazine' by Smith, Kline and French Laboratories), 5 mg and 10 mg t.i.d. along with placebo medication (Lactose), with the following objectives in view:

1. To estimate the proportion of placebo reactors among patients reporting symptoms of radiation sickness.
2. To determine the extent to which the proportion of placebo reactors is related to: (a) the locus of irradiation (i.e. above and below diaphragm), (b) the day of onset of symptoms, (c) the order of treatment with placebo and trial anti-emetic compounds.
3. To evaluate, if possible, the effectiveness of prochlorperazine as an anti-emetic for radiation sickness and determine the extent to which its efficacy is related to: (a) patient classification variables, (b) the order of treatment with placebo and trial compounds, (c) dose (5 mg vs 10 mg t.i.d.).

Method of study

Although the syndrome of radiation sickness is said to include a variety of symptoms: nausea, vomiting, anorexia, malaise, prostration, headache, dizziness, and weight loss, it was felt that we could accurately base our diagnosis only on the first two (i.e. nausea and/or vomiting). In deference to the plea

Table 1

Pattern of medication

Day entering study	Envelope No 0	Envelope No 1	Envelope No 2	Envelope No 3
Monday	0	Drug trial No 1 for 3 days	Placebo for 4 days	Drug trial No 2 for 3 days
Tuesday	0	for 3 days	» for 3 days	for 3 days
Wednesday	0	for 3 days	» for 2 days	for 3 days
Thursday	Placebo for 4 days	for 3 days	» for 4 days	for 3 days
Friday	» for 3 days	for 3 days	» for 4 days	for 3 days

of other authors (ELLIS and STOLL) it was decided to attempt to evaluate the symptoms of anorexia and lassitude individually

It has never been our practice to give anti emetics throughout the course of radiation therapy as a prophylactic measure against radiation sickness We do not agree furthermore that this eliminates the psychic element as stated by other authors (SILVERMAN et coll)

Any patient receiving radiation therapy to any area of the trunk at our institute and reporting symptoms of radiation sickness was eligible for inclusion in this study A patient was excluded only when the radiation sickness was judged so severe as to interfere with the course of radiation therapy

Subjects were classified on the basis of two variables locus of radiation (above or below the diaphragm) and day of the week entering study Accordingly there were ten subject groups two for each of five days Patients could not enter the study on Saturday or Sunday

A placebo compound (Lactose) and two dosage levels (5 and 10 mg) of prochlorperazine were used as treatment drugs All were prepared in No 2 pink capsules and dispensed in envelopes distinguishable only by number A drug trial consisted of three capsules daily on three consecutive days

Every subject was to experience a three day trial of two different compounds one of placebo and one of either 5 mg or 10 mg of prochlorperazine Both orders of these two drug combinations were used equally often The resulting four treatment groups are identified by letter below

Group	First trial	Second trial
A	Placebo	5 mg prochlorperazine
B	5 mg prochlorperazine	Placebo
C	Placebo	10 mg prochlorperazine
D	10 mg prochlorperazine	Placebo

Placebo capsules were given on certain days in addition to the trial period as shown in Table 1

The use of placebo capsules on week ends and initially for patients entering the study on Thursday or Friday was known to the medical staff however it

Table 2

Patients excluded from study

Reason for exclusion	Site of radiation Above diaphragm	Below diaphragm	Total
Did not follow instructions	2	3	5
Complications in patient's condition	3	0	3
Response pattern to pills not interpretable	2	0	2
Unreliable history of symptoms	0	1	1
Radiation therapy discontinued	1	2	3
Patient refused to continue medication	0	1	1
Total	8	7	15

was not known to them that in any of the drug trials placebo capsules were also used Before starting the second drug trial, the patient was withdrawn from the study for a period of at least 48 hours if his symptoms had disappeared If symptoms reappeared the second drug trial was begun

Patients were allocated to the treatment groups as follows within successive sets of four individuals, one was randomly assigned to each treatment group, and assignment in one subject category was independent of every other The order of assignment of patients to treatment groups was not known to the medical personnel Treatment was assigned by taking the first unused envelope from an appropriate prearranged set Ten sets of envelopes, one for each subject category, were used

The envelopes were identified only by serial number and subject category, each containing the correct number of capsules to supply one patient throughout the study period

The patients were interviewed daily throughout the course of study to obtain an evaluation of symptom severity and toxic effects Evaluations were recorded on individual forms prepared for this purpose

Results and Discussion

An attempt was made to evaluate the symptoms of anorexia and lassitude individually, and in combination with the symptoms of nausea and vomiting This proved to be unproductive in large part because many of the patients had suffered from these symptoms for some time preceding the onset of radiotherapy In some cases this could be ascribed to the extent of the disease and in some to their apprehension in the knowledge that they suffered from malignant disease Therefore, the results reported are based on relief of the symptoms of nausea and vomiting

Of the 126 patients who initially displayed symptoms of radiation sickness, only 52 completed the series of two drug trials Fifteen patients were excluded

Table 3

Patients not completing sequence of drug trials

Reason for not completing study	Site of radiation Above diaphragm	Below diaphragm	Total
No recurrence of symptoms between trials	7	24	31
Radiation therapy discontinued	5	13	18
Complications unrelated to drug therapy	2	3	5
Patient refused further medication	0	2	2
Did not follow instructions	0	2	2
Patient expired before study ended	1	0	1
Total	15	44	59

from the study for the reasons shown in Table 2 and do not appear again in any further tabulations or in any of the conclusions drawn about placebo or drug effects

Of the remaining 111 patients who completed at least one drug trial of the sequence and who contributed usable information to the study, 59 did not complete the full sequence of trials The reasons for this attrition of the series through noncompletion are given in Table 3 As seen the most frequent cause of noncompletion is the failure of the patient to redevelop symptoms of radiation sickness between drug trials on days when no pills were given If no further symptoms developed when the medication was withdrawn the trial was stopped since there were no symptoms against which to evaluate drug response The 18 patients who discontinued radiation therapy before completion of the drug trial were those who did not develop symptoms of radiation sickness until later in the course of radiotherapy or those who had courses of radiotherapy shorter than originally foreseen Of the complications there were four cases of severe and protracted vomiting (three irradiated below the diaphragm) and one case of cardiac decompensation

A patient was deemed to have an unequivocal response (++) if his or her symptoms of radiation sickness disappeared during administration of any one compound No response was recorded as (— —) As seen from Table 1 patients entering the study on Thursday or Friday received an initial few days of placebo medication and then proceeded with Drug trial I Since all patients completed at least the first Drug trial plus Envelope 2 of placebo medication it was possible to obtain an indeterminate response If there was any doubt about the response of a patient to medication this was recorded as (+—) This situation arose when symptoms disappeared during administration of one compound were held in abeyance during the administration of the succeeding compound, and then did not reappear when all medication was withdrawn This occurred in twenty cases If a similar study were to be conducted in the future we feel it would be advisable to allow a lapse

of time between each medication whenever symptoms disappeared during administration of the first medication This would eliminate the indeterminate groups

In the series of 52 cases, who completed the entire sequence of drug trials, there were two patients who responded completely to the initial placebo medication started on Thursday or Friday, and did not redevelop symptoms before starting Drug trial 1 on Monday Response to prochlorperazine in Drug trial 1 is therefore considered ambiguous Two cases in this group were also inadvertently started on Drug trial 2 without a lapse of 48 hours without drug to see if symptoms would reappear Both of these cases received placebo medication in Drug trial 2, and since their response had been interpreted from previous medication, this trial was disregarded

In the series of 59 cases who did not complete the entire sequence of drug trials, but did complete the first drug trial, some information can be obtained from each patient Again, six patients entering the study on Thursday or Friday responded completely to the initial placebo medication and therefore their response to prochlorperazine given in the first drug trial is considered ambiguous Ten patients responded completely to prochlorperazine in the first drug trial, and therefore their response to the placebo spacer (Envelope 2) was considered ambiguous, even though they did not redevelop symptoms when all medication was withdrawn In the entire series, there were 78 patients in whom a response to both prochlorperazine and the placebo could be evaluated Fifty one (65 5 %) responded to the drug, but many of these also responded to the placebo Eight (10 %) were classified as an indeterminate response Nineteen cases (24 4 %) showed no response to the drug Thirteen of this latter group showed no response to placebo either, but six cases were classified as placebo reactors

On further review of these six cases, it is felt that in only one case was there an unequivocal response to placebo and an actual increase in symptoms when the patient was receiving prochlorperazine This seeming contradiction may be explained by the fact that the radiation dosage was increased the day prior to the switch to prochlorperazine Two of the remaining five cases experienced very mild nausea while receiving prochlorperazine, for which they were classified as non reactors The three other cases responded to placebo at one point but failed to respond to placebo at another point These might have been classified as indeterminate responses

Placebo reactors Response to placebo medication given initially to those patients entering the study on Thursday or Friday could be classified as effective (++) or ineffective (— —) depending upon whether symptoms disappeared or remained Response to placebo medication given after Drug trial 1 as a spacer could be judged effective only if the patient still experienced symptoms after Drug trial 1 If the patient did not have symptoms on the

Table 4

Percentage of placebo reactors classified by site of radiation

Site of radiation	No of patients	Percentage placebo reactors ++ only	Percentage placebo reactors ++ and +−	Average cumulative integral dose of radiation received (megagram rads)
Above diaphragm	30	70 0	76 6	7 1
Below diaphragm	81	58 0	70 3	11 5
Total	111	61 3	72 1	10 3

completion of this trial but redeveloped symptoms during the placebo spacer, then the placebo was judged ineffective The possibility of an ambiguous response (+−) has already been discussed Computations of the proportion of placebo reactors are based on both the (+ +) group and a combination of the (++) and (+−) groups

Placebo effect and site of irradiation The percentage of placebo reactors for the total series classified by the site of radiation is shown in Table 4 The percentage of placebo reactors in the 111 patients ranges between 61 and 72 depending on whether or not the (+−) group is counted The true percentage of placebo reactors for this sample of 111 patients lies somewhere between these two percentages Since this series of 111 patients may also be regarded as a sample from some population of radiation therapy patients sampled through time it would be possible to compute confidence limits for the percentage of placebo reactors in this conceptual universe However because of the presence of the indeterminate group we have not attempted to compute confidence intervals for the group as a whole or for any subgroups

The percentage of placebo reactors is seen to be higher for those radiated above the diaphragm While this difference is not statistically significant even when we use the most extreme estimates of percentage placebo reactors for the two groups (76 6 % for the group radiated above the diaphragm and 58 0 % for the group radiated below the diaphragm) the difference in rates shows a relationship with the average cumulative integral doses of radiation received by each group (Table 4) If there is a physiologic effect of radiation therapy causing nausea and emesis in those exposed to it we should expect this effect to be more marked in the individuals receiving larger cumulative integral doses of radiation

We should also expect the percentage of placebo reactors to be less in this latter group since there is a real biologic effect present so that the physiologic component might outweigh any psychologic component as a factor affecting the production of symptoms of radiation sickness

Placebo effect and dose of radiation received Since the placebo is thought to be most effective when the psychologic components of the disease are of greater

of time between each medication whenever symptoms disappeared during administration of the first medication This would eliminate the indeterminate groups

In the series of 52 cases, who completed the entire sequence of drug trials, there were two patients who responded completely to the initial placebo medication started on Thursday or Friday, and did not redevelop symptoms before starting Drug trial 1 on Monday Response to prochlorperazine in Drug trial 1 is therefore considered ambiguous Two cases in this group were also inadvertently started on Drug trial 2 without a lapse of 48 hours without drug to see if symptoms would reappear Both of these cases received placebo medication in Drug trial 2, and since their response had been interpreted from previous medication, this trial was disregarded

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Table 7

Percentage of placebo reactors classified by sex

Sex	No of patients	Percentage placebo reactors ++ only	Percentage placebo reactors ++ and +−	Average cumulative integral dose of radiation received
Male	24	50 0	54 1	6 6
Female	87	64 3	77 0	11 3
Total	111	61 3	72 1	10 3

average cumulative integral dose of radiation received by each sex and the percentage of placebo reactors In contrast to the relationships found between average cumulative integral dose of radiation and percentage placebo reactors for those radiated above and below the diaphragm (discussed in the preceding paragraphs) a high average cumulative integral dose of radiation for females is accompanied by a high proportion of placebo reactors while a low average cumulative integral dose of radiation for males is accompanied by a low proportion of placebo reactors This apparent contradiction to the results found for the groups radiated above and below the diaphragm can be partially resolved by examining the integral dose placebo relationship for males and for females separately in those radiated above and below the diaphragm The resulting four fold table (Table 8) gives the proportion of placebo reactors and the average cumulative integral dose of radiation received for each of the four groups males radiated above the diaphragm males radiated below the diaphragm females radiated above the diaphragm and females radiated below the diaphragm

It can be seen that the expected inverse relationship between average cumulative integral dosage and percent placebo reactors holds for females only For males a slight decrease in average cumulative integral dose from 7 6 to 4 7 megagram rads from the above the diaphragm to the below the diaphragm group is accompanied by a large decrease in the proportion of placebo reactors from 63 % to 25 % The proportion of male placebo reactors radiated below the diaphragm (25 %) is determined on only eight patients,

Table 8

Percent placebo reactors (++ only) and average cumulative integral dose of radiation received as classified by site of radiation and sex of patient

	Site of radiation					
	Above the diaphragm		Below the diaphragm		Total	
Sex	Percent placebo reactors	Average cumulative integral dose	Percent placebo reactors	Average cumulative integral dose	Percent placebo reactors	Average cumulative integral dose
Male	63	7 6	25	4 7	50	6 6
Female	79	6 5	6?	12 3	64	11 3
Total	70	7 1	58	11 5	61	10 3

Table 5

Percentage of placebo reactors classified by cumulative integral dose of radiation received up to first symptoms of radiation sickness

Cumulative integral dose (megagram rads)	No of patients in the group	Percent placebo reactors (++ only)	Percent placebo reactors (++ and +−)
0— 3.9	36	67	72
4— 7.9	19	68	79
8—11.9	20	55	80
12—19.9	18	67	67
20 and over	18	50	61
Total	111	61.3	72.1

importance, we should then expect to see a higher proportion of placebo reactors in the group with the lowest average cumulative integral dose. This is in fact the case, as noted both in Table 4 where the group receiving the highest average cumulative integral dose of radiation has a smaller proportion of placebo reactors than does the other group, and in Tables 5 and 6 where there is seen to be some relation between an increasing size of both cumulative integral dose and daily integral dose with a decreasing proportion of placebo reactors. The trend seems to be clearer where the indeterminate group has been included. This might have been more clearly shown if more patients had been included in each group.

Placebo effect and sex. Another factor which has some association with the proportion of placebo reactors is sex. The proportion of males and females who are placebo reactors is shown in Table 7 along with the average cumulative integral dose of radiation received. Again, one sees a relationship between the

Table 6

Percentage of placebo reactors classified by daily integral dose of radiation received up to first symptoms of radiation sickness

Daily integral dose (megagram rads)	No of patients in the group	Percent placebo reactors (++ only)	Percent placebo reactors (++ and +−)
0.0 to 0.49	6	50	83
0.5 to 0.99	16	56	63
1.0 to 1.49	14	79	86
1.5 to 1.99	36	69	81
2.0 to 2.49	15	53	60
2.5 to 3.99	14	50	57
4.0 and over	10	50	50
Total	111	61.3	72.1

Placebo effect and order of medication The placebo reactors in the group of 78 patients are classified in Table 10 by the order in which the medications were given The 33 subjects who received placebo only has been excluded The percentage of placebo reactors is higher for those patients who received the placebo first than for those who received prochlorperazine first but when the indeterminate group (+—) is included this difference becomes insignificant It is reasonable to assume that the placebo reactor rates should be similar and not vary with the order of medication Thus it would appear that the addition of the indeterminate group may give us a truer estimate of the placebo reactor rate

Effect of prochlorperazine on non placebo reactors There were 31 non placebo reactors included in the entire series Ten of these cases never received prochlor perazine leaving 21 cases in which evidence is available as to the effects of this drug in 5 mg and 10 mg individual doses No attempt is made to further divide this group of patients as was done for the total series of 111 patients because of the already small size of the group Of the 21 non placebo reactors eight (38 %) responded to prochlorperazine Eight patients received the 5 mg dosage to which two responded Thirteen patients received the 10 mg dosage to which six (46 %) responded No significance is attached to these findings because of the very small number of patients involved

Conclusive comment Because of the apparently general belief that patients undergoing radiotherapy very frequently suffer a significant degree of radiation sickness we feel that these results should be disseminated as widely as possible in the hope that this will tend to reduce the alarming reports of this condition which almost inevitably reach the patient before his first visit to the radiotherapist It has been our experience that physicians and nurses are as fre quently misinformed regarding the severity and frequency of this syndrome as are lay persons

SUMMARY

A m thod for determining the proportion of placebo reactors in a double blind study of patients receiving medication for radiation si kness is described The proportion of placebo reactors l es between 61 and 7? The factors which most closely affect this proportion are the site of irradiation sex of patient and (total) cumulative integral dose of radiation No evaluation of the effectiveness of prochlorperazine as an anti-emetic was attempted because of the small number of cases involved

ZUSAMMENFASSUNG

Die Verfasser beschreiben eine Methode zur Bestimmung des Anteiles von Plazebo-Reaktoren in einer doppeltbl nden Studie von Patienten welche Medizin fur die Strahlen krankheit erh elten Die Proport on der plazeboreagierenden Personen liegt zwisch n 61 o un l 72 Die Faktoren welche besonders auf dieses Verhaltnis einwirken sind der Ort der

Table 9

Percentage of placebo reactors classified by day of week on which symptoms were first experienced

Day of week	No of patients	Percentage placebo reactors ++ only	++ and +−
Monday	18	55 5	77 7
Tuesday	29	62 0	65 5
Wednesday	17	70 5	76 4
Thursday	16	68 7	68 7
Friday	19	47 4	68 4
Saturday	7	57 1	71 4
Sunday	5	80 0	100 0
Total	111	61 3	72 1

so that some caution must be placed on the interpretation of this percentage, and the corresponding average cumulative integral dose based on these patients One further point is that '3' of the eight patients in this group was in fact a single patient who was treated at three widely spaced points in the study period and who responded to neither placebo nor Compazine even though receiving a small cumulative integral dose (average of 0 620 megagram rads) at each visit If this patient's results are treated as a single case rather than as three separate cases the proportion of placebo reactors is raised from 25 % to 33 % and the average cumulative integral dose is raised from 4 7 megagram rads to 5 67 megagram rads

Placebo effect and the day of first symptoms The percentage of placebo reactors, classified by the day of the week on which symptoms were first noted, is given in Table 9 There does not seem to be a simple pattern for the variation in percent placebo reactors throughout the week Earlier in the paper, it was hypothesized that the length of time a patient received radiation therapy after a period of rest from irradiation (in this case the week end, since no routine radiation therapy is given on Saturday or on Sunday), would provide an index of recent exposure which might correlate negatively with the proportion of placebo reactors The data in Table 9 are not consistent with such a hypothesis and give the impression of random fluctuations about the mean of the total series

Table 10

Percent placebo reactors classified by order of medication

Order of treatment	No of patients	Percentage placebo reactors ++ only	++ and +−
Placebo first	45	78 %	78 %
Compazine first	33	30 %	66 %
Total	78	57 7 %	73 2 %

FROM DEPARTMENT 1 RESEARCH INSTITUTE OF NATIONAL DEFENCE SUNDBYBERG, SWEDEN

RADIOPROTECTIVE EFFECT OF AMINOALKYL THIOESTERS

by

BERTIL HANSEN and BO SORBO

In a previous communication from this laboratory (HOLMBERG and SORBO 1959) the radioprotective effect of 2 aminoethyl thiosulfuric acid was reported The present paper describes an extension of this work to some other aminoalkyl thioesters

Materials The sodium salts of sulfocysteine and aminoethyl thiophosphoric acid (sodium hydrogen S (2 aminoethyl phosphorothioate) were synthesized by previously described methods (SORBO 1958 ÅKERFELDT 1959)

The S (3 aminopropyl) thiosulfuric acid was prepared according to the directions given by BRETSCHNEIDER (1950) for the synthesis of the aminoethyl ester except for the fact that the propyl compound was recrystallized from water ethanol (Anal calculated for $C_3H_{10}NO_3S_2$ C 21 0, H 5 27 Found C 20 8 H 5 5)

The S (2 aminoethyl) ethanethiosulfonate hydrobromide was prepared as follows 4 98 g sodium ethanethiosulfonate and 6 15 g 2 bromoethylammonium bromide were boiled for 5 hours in 30 ml isopropanol and left over night The precipitated sodium bromide was filtered off and washed with a few millilitres isopropanol Diethyl ether was gradually added to the combined filtrate and washing, whereupon light brown crystals were obtained As the product was contaminated with sodium bromide it was treated with

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Bestrahlung das Geschlecht der Patienten und die kumulative Integraldosis der Strahlung Eine Bewertung der Wirksamkeit des Prochlorperazin als Antiemetikum wurde wegen der geringen Anzahl der Fälle nicht versucht

RÉSUMÉ

Les auteurs décrivent une méthode de détermination par une 'double blind study' de la proportion de sujets réagissant au placebo dans une série de malades recevant un traitement pour un mal des rayons La proportion d'ensemble de sujets réagissant au placebo est entre 61 et 72 % les facteurs qui influent le plus sur cette proportion sont le lieu de l'irradiation le sexe du sujet et la dose intégrale cumulative totale de radiations Le petit nombre des cas étudiés n'a pas permis d'essayer de juger l'efficacité de la prochlorpérazine comme anti émétique

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Table 2

Radioprotective effect of aminoalkyl thioesters

Compound	Dose mg/kg	30-day mortality %
None	—	95
Cysteamine HCl	200	5
Aminopropyl thiosulfuric acid	250	60
Sulfocysteine	1 600	100
Aminoethyl ethanethiosulfonate HBr	35	100
Aminoethyl thiophosphoric acid	400	5
Aminoethyl ethanethiophosphonate	70	98

Results

The acute toxicity of the compounds to be used in the irradiation experiments was first determined (Table 1) following which the compounds were tested as radioprotectors at a dose level of about 0.5 LD_{50}. The effect on the 30 day mortality after irradiation is shown in Table 2, from which it is evident that aminopropyl thiosulfuric acid has a protective effect but is inferior to that of cysteamine. The protection appears to be of the same magnitude as that previously reported for the aminoethyl compound (HOLMBERG & SORBO). Introduction of a carboxyl group in the alkyl chain of the thiosulfate ester (sulfocysteine) destroys the protective action of the latter. Aminoethylthiophosphoric acid on the other hand showed a strong protective effect, at least as good as that of cysteamine. The practical use of this compound as a radioprotective agent will be further studied. If one of the oxygen atoms in the active thiosulfate or thiophosphate esters is replaced by an alkyl group, thereby giving a thiosulfonate or thiophosphonate ester, the toxicity of the parent compound is increased and the protective action disappears.

The protective effect of aminoethyl thiosulfuric acid and aminoethyl thiophosphoric acid demonstrated in this and previous work merits some consideration. Evidence has previously been obtained for the conversion of the thiosulfate ester to mixed disulfides of cysteamine and proteins (SORBO). This could explain the protective properties of the thiosulfate ester, especially in view of the theories put forward by ELDJARN and PIHL. The thiophosphate has been shown to be split enzymatically to cysteamine (ÅKERFELDT), which could explain the protective action of this ester. It is also possible that the thiophosphate reacts directly with proteinbound sulfhydryl groups to give mixed disulfides. Of interest is the fact that aminopropyl thiosulfuric acid was somewhat more toxic than the aminoethyl compound, but had a comparable protective effect. A similar relationship has been found for the corresponding mercaptans (DOHERTY et coll.). The complete disappearance of protective action after the introduction of a carboxyl group in the thiosulfate ester is on the other hand not observed with the corresponding mercaptans (DOHERTY

Table 1

Acute toxicity of aminoalkyl thioesters

Compound	Formula	LD_{50} g/kg
Cysteamine HCl	$NH_2C_2H_4SH{,}HCl$	0.45 ± 0.01
Aminopropyl thiosulfuric acid	$NH_2C_3H_6SSO_3H$	0.[illegible]8 ± 0.02
Sulfocysteine (Na salt)	$CO_2HCH(NH_2)CH_2SSO_3Na$	0.32 ± 0.01
Aminoethyl ethanethiosulfonate HBr	$NH_2C_2H_4SSO_2C_2H_5\ HBr$	0.056 ± 0.00[illegible]
Aminoethyl thiophosphoric acid (Na salt)	$NH_2C_2H_4SPO_3HNa$	0.93 ± 0.03
Aminoethyl ethanethiophosphonic acid	$NH_2C_2H_4SPO_2HC_2H_5$	0.14 ± 0.003

boiling n-butanol-ethyl acetate (3:1), filtered, and the thiosulfonate precipitated from the filtrate by addition of more ethyl acetate. The precipitate was dissolved in 15 ml hot n-butanol, and treated with active carbon. After cooling, 0.9 g (yield 12 %) of pure crystalline product was obtained. (*Anal.* calculated for $C_4H_{12}BrNO_2S_2$: C 19.2, H 4.84. Found: C 18.8, H 4.72.) The compound was found to be rapidly hydrolyzed in water solution ($k = 3.52 \cdot 10^{-4}$ sec^{-1} in 0.1 M KCl at pH 7.00 and 25° C).

Aminoethyl ethanethiophosphonic acid: S-(2-ammoniumethyl) ethanephosphonothioate) was prepared as follows: 9.5 g disodium ethanephosphonothioate and 12.0 g 2-bromoethylammonium bromide were dissolved in 10 ml water. After a week at room temperature, 5 g (53 % yield) of crystalline product had formed. It was recrystallized from water, and dried over phosphorus pentoxide in vacuo. (*Anal.* calculated for $C_4H_{12}NO_2PS$: C 28.4, H 7.14. Found: C 28.4, H 7.12.)

The mice used in this investigation were males of an inbred CBA strain. Their body weight was about 20 g.

Methods. Total body roentgen irradiation was delivered from a material testing roentgen machine, operated at 260 kV and 10 mA, using filter 4 mm Al and 0.5 mm Cu. The focus target distance was 40 cm, and the dose rate about 84 r/min. The animals were kept in plastic cages during the irradiation. The roentgen dose given was 1 092 r (the LD_{50} for the mice used was 748 r).

Each group of animals treated with the different compounds consisted of 10 animals, except in case of sulfocysteine for which only 17 mice were used. Cysteamine hydrochloride was used as a reference substance. The compounds to be tested were injected intraperitoneally in saline solution 15 minutes before irradiation. The volume injected was kept constant at 0.3 ml per animal.

The LD_{50} for the compounds was determined according to MILLER and TAINTER (1944) after intraperitoneal injection in saline solution (0.3 ml per animal).

FROM THE DEPARTMENT OF PAEDIATRICS UNIVERSITY OF OTTAWA CANADA

GENETIC HAZARDS OF RADIATION TO MAN
PART II

by

PAUL DE BELLEFEUILLE

The first part of the present paper was published recently (DE BELLEFEUILLE 1961) in this journal

Existing levels of radiation

In the estimation of genetic hazards attempts are made to establish the amount spread over the whole population received by the human testis or ovary from conception to the age of 30 years, by which time one half of all offspring have been procreated

Natural radiation from the ground from cosmic rays and from potassium 40 in human tissues represents a 30 year gonad dose of the order of 3 r (MRC Report) to 4 3 r (see Genetic Effects of Atomic Radiation) It is in the light of this estimate that one may appraise the significance of man made radiation impinging upon human germ plasm

Fall-out from test detonations of nuclear weapons consists of a large number of radio-nuclides liberated into the atmosphere (LAPP 1959) These present a two fold genetic danger External radiation comes to the gonad from the ground internal radiation is due to isotopes which are incorporated into human tissues Of these the bone seekers (strontium 89 and 90, plutonium 239) emit short range β particles they are thus much less significant in terms of genetic effects than in relation to the induction of leukaemia and bone

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et coll, PATT et coll) since cysteine has a protective effect, although an inferior one to that of cysteamine. The absence of protective action from ethanethiosulfonate and ethanethiophosphonate is probably explained by the comparatively high toxicity of these compounds. Although they can be expected to liberate cysteamine in vivo, the amounts of this compound that can be formed are too small to be effective for protection against roentgen radiation.

Acknowledgement

The authors wish to express their sincere thanks to Dr A. NELSON for permitting the irradiation experiments to be carried out in his department. Able technical assistance was given by Mrs I. B. HENRIKSSON.

SUMMARY

*Certain aminoalkyl thioesters have been investigated as radioprotective agents. Amino*ethyl thiophosphoric acid (as the sodium salt) with a protective effect comparable to that of cysteamine was the most effective of the compounds studied.

ZUSAMMENFASSUNG

Bestimmte Aminoalkylthioester wurden auf ihre Eignung als Strahlenschutzmittel untersucht. *Aminoäthylthiophosphorsaure (als Natriumsalz) mit einer Schutzwirkung die der*jenigen des Cysteamin vergleichbar ist, erwies sich als die wirksamste der untersuchten Verbindungen.

RÉSUMÉ

Les auteurs ont étudié l'effet radioprotecteur de certains aminoalkyl thioesters. L'acide aminoéthyl thiophosphorique sous forme de sel sodique ayant un effet protecteur comparable à celui de la cystéamine est le plus efficace des corps étudiés.

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Table 4

Reported cases of unwitting irradiation of an embryo in the treatment of infertility by ovarian roentgen irradiation

Author	Time of gestation	Dose	Effect on child
KAPLAN 1939	About 2 months? (1 case)	66 ± 16 r	Stillborn hydrocephalic distorted features rudimentary nares extreme polyhydramnios
ROLAND & WEINBERG 1959	2 and 3 weeks (1 case)	Estimated to uterus 18 r	Apparently well child at age 6 months
ISRAEL 1952	1 and 2 weeks (1 case)	To ovaries 200—300 r	Microcephalic child, died at 2 months

that for the general population the maximum permissible dose of man made radiation to the gonads from conception to the age of 30 years be set below 6 r It is easy to see that with only a few roentgen examinations this limit can be exceeded for an individual and that present practices do, in fact approach the danger point for the population as a whole Strictly from the genetic view point all radiation is unsafe and it may well be that even the tolerance just cited is too lax In any case the increasing accessibility of, and recourse to roentgen rays as a diagnostic aid make it imperative that physicians do the utmost to limit the doses space the examinations employ radiography rather than fluoroscopy whenever possible, and insist on proper shielding of parts of the body not being examined (TURPIN et coll 1957) Present work on intensifying screens for example is encouraging one may hope that a reduction to small fractions of the present doses shall soon be possible This is of particular importance in view of the fact that gonad doses from industrial atomic power will soon have to be reckoned with

In radiotherapy doses are of course much higher but applied to a much smaller fraction of the population mostly to persons who are past the reproductive age Thus the effect of radiotherapy on the total population genetic dose is small It is evidently most important to avoid any therapeutic irradiation of the human gonads before the end of the reproductive age Now abandoned one hopes is the practice of giving so called stimulating doses of roentgen rays to the ovaries of amenorrhoeic females who wish to conceive As late as 1957 however KAPLAN claimed to have shown the absence of genetic ill effects of this procedure in 564 women so treated True he admitted one mother died of leukaemia one year later and one child was unwittingly irradiated when already conceived and was born quite abnormal Here lies the most obvious danger of this form of treatment for barrenness that of damaging the child of a woman who does not realize that she is pregnant, this accident has been reported in 3 cases (Table 4) in 2 of which the result for the child was disastrous The very high susceptibility of the embryo to the teratogenic effect of roentgen rays is illustrated by the experiments of MURAKAMI and KAMEYAMA (1958) on the mouse from which it is possible to calculate a

sarcoma through irradiation of contiguous cells But other radionuclides have been found to emit γ rays from soft tissue, amounting to a 30 year gonad dose of 0 018 to 0 15 r according to geographical location (STEWART 1958, MARLEY 1958, LIBBY 1958) The principal of these isotopes is believed to be cesium 137, which, being metabolized much like potassium, is found in all cells, including gonadal cells Fortunately, this isotope's actinic half life is only 20 days, and the biological half life only 70 days (MORGAN 1959), its significance thus depends mainly on the continued ingestion of it, which in turn varies with the rate of fall out This should tend to decrease with time, provided tests do not continue Less well documented, but perhaps more disturbing in its implications, is the case of carbon 14, which emits β rays and has a half life of 5 600 years (LEWIS 1957) Not only could this isotope exert genetic effects upon the host's genes, but it could, itself, be handed down with the germ plasm for an indefinite number of generations (PAULING 1958)

The total 30 year gonad dose from fall out products, both internal and external, was estimated in the U N Report (1958) at 0 01 r if the tests stopped in 1958, but could reach as high as 0 12 r if the tests were to be continued at the same rate Thus the expected hazard from fall out lies between 0 3 % and 4 % of the hazard from natural radiation The magnitude of the genetic effects to be expected from this added load of ionizing radiation must depend upon the determination of the mutation doubling dose for man This will be discussed later

Medical use of ionizing radiation At the request of the United Nations, estimates of the gonad dose spread over the whole population from present practices in diagnostic radiology have been prepared in various countries Expressed as percentages of the natural background radiation, these estimates range from 22 % in Britain (MRC Report 1956), through 72 % in Sweden (LARSSON 1958), to a little more than 100 % in the U S A (Nat Acad Sci 1956) A more recent British estimate (Adrian Report 1960) is lower than the earlier one (14 %, plus 5 % for radiotherapy — which did not enter into any of the previous estimates) This lower figure is stated to result from more accurate determinations, perhaps it also reflects increased care on the part of physicians, due to new awareness of genetic hazards

While many examinations do not result in significant irradiation of the gonads, procedures in which the latter are involved in the direct ray entail considerable genetic doses For example, intra venous pyelography, when done with maximum precautions, delivers 1 29 r to the female gonads, and 3 21 r to the foetus' gonads when a pregnant woman is examined (OSBORN 1956) Present methods of fluoroscopy deliver from 3 to 77 r per minute to the patient (ROBINOW & SILVERMAN 1957) in abdomino pelvic examinations, a large dose reaches the ovaries or testes The meaning of these figures can be appreciated from the recommendation, made in the MRC Report (p 64),

Table 5

Mutation doubling dose Various estimates having a bearing on the probable value for man

Author	Estimated doubling dose	Basis of estimate
CHARLES* 1950	24 r	All mutations in mice Control mutation rate (1 1 × 10^-)/ regression coefficient per r (4 48 × 10^-) = 24 5 (See also Part I Fig 2)
W L RUSSELL 1954	30 r *	Recessive mutations in mice Control mutation rate (5 3 × 10^-)/induced rate per r (1 75 × 10^-) = 30 3
BATEMAN 1956	40 r * (mean)	Lethals in mice Varies between 25 and 47 r according to stage in spermiogenesis
MULLER 1955	37 r	Estimated for mice applicable to man see source
MRC Report 1956 pp 42—45	30—80 r	Limits between which the true value probably lies reasoned from results of experiments on various species
HALDANE 1955	A little more than 3 r	Hypothesis that most human mutations are due to radiation
FRITZ NIGGLI 1956	7 r	For some dominant lethals in mice
	80 r	For some recessives in mice Two extreme figures which probably enclose the human doubling dose
LEJEUNE & TURPIN 1957 p 495	30 r	Reduction in masculinity of offspring due to irradiation and due to age (see text)
COURT BROWN & DOLL 1956 (MRC Report p 87)	30—50 r	Doubling dose (to spine) for leukaemogenesis in man linear effect likened to somatic mutation
BENDER 1957	33 r	For chromosome breaks in normal human diploid somatic cells in tissue culture (somatic mutation)
MORTON 1960	25 r	For sex linked lethals in man from sex *ratio changes* in offspring of women atomic bomb survivors
Present review	*31.8 r*	New analysis of atomic bomb data in ABCC Report (See Table 7)

Result of chronic irradiation all other data cited are based on acute exposure
Not given by author calculated from his data.

tions equal to the number occurring naturally The size of this doubling dose (denoted henceforth by D_d) is evidently related to that portion of the spontaneous mutations which is due to natural background radiation (internal and external) to the gonads The greater this portion the smaller the D_d It cannot evidently be determined directly in man by experiment But various estimates have been made for the value of D_d applicable to man some are quoted in Table 5 The bases for these estimates vary widely Some are derived from experiments on the mouse which has roughly the same DNA mass per germ cell as man One estimate ingeniously compares the effect of parental

'doubling dose' of 13 r for the induction of *central nervous system malformations* In man, irradiation of the foetus early in gestation during radiotherapy for uterine conditions (ZAPPERT 1926), or by atomic bombs (YAMAZAKI et coll 1954, MILLER 1956), is known to produce microcephaly Excluding the occurrence just referred to, KAPLAN reports only 2 malformed children (one Hirschprung's disease, one hydrocephalus with spina bifida) in the first generation of 413 live born from 564 mothers treated before conception, and none malformed among 23 second generation offspring (born to children conceived following treatment) This amounts to an incidence of malformations of only 0 46 % *among 436 children, and* KAPLAN *glowingly* points to this as proving the harmlessness of the procedure One may wonder why he does not go one step further and claim that pre *conception irradiation of the ovaries* actually decreases the hazard of having abnormal children The data as given cannot be appraised, since the manner of examination of the children, or of otherwise collating information about them, is not stated The sex distribution is given, however, for 409 children in the first generation (excluding the 2 malformed ones and 2 who died of acquired conditions), among whom there were only 191 males a remarkably low sex ratio (i e males/total) of 46 70 % This figure, as well as that for malformations, should be compared with data from a control group of mothers matched for age, parity and racial origin *Such data are absent from the study as published, but the low sex ratio strongly* suggests that maternal irradiation before conception did, in fact, affect germ cells in an adverse way (see Part I, Fig 1) What it does, otherwise, to the ovary, apparently to produce a return of fertility, is not known There is no such thing, in fact, as a stimulating effect of ionizing radiation, apart from the reactions to injury Further, the claims for the effectiveness of this empirical procedure are based on uncontrolled studies (ISRAEL 1952, KAPLAN 1957) Indeed, JEFFCOATE (1952) of Liverpool pointed to a spontaneous cure rate of about 60 % for similarly selected cases of amenorrhoea, even of some years *standing, in women of less than 30 years of age*

Discussion

It is not possible to state the number of genes constituting man s hereditary endowment, nor do we know with any precision how frequently these undergo mutation, severally or as a whole, or in what way accidents in human reproduction and survival to maturity are related quantitatively to mutation, natural or induced Two approaches to this problem, one theoretical and one empirical, suggest themselves

1 The theoretical model

The simplest, and most useful, expression of the mutational damage accruing to man's germ cells through ionizing radiations would be the doubling dose that is, the amount of radiation causing an additional number of muta

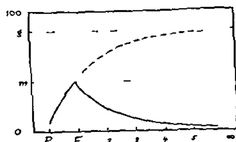


Fig 5 A theoretical model showing the percentage increase in the incidence of pre natally caused diseases and anomalies expected in each generation following the application of D_2 to the P only (full curve) or the permanent doubling over a number of generations of the mutagenic load (broken curve) Based in part on PENROSE (1956)

of estimates will be seen to fall rather below 30 r At this time therefore, it seems that the natural dose to the gonads of 3 r per 30 years (MRC Report 1956) accounts for about one tenth or perhaps a little more of the mutations occurring naturally in man

The mutational moiety in the causation of sterility abortion stillbirth and neo natal death as well as in various constitutional illnesses of later life is probably considerable but its magnitude cannot at this time be appraised By contrast overt malformations and those diseases which display a notoriously hereditary mode of transmission though reflecting only a part of the total load of mutations afford the only fairly confident approach to an estimate of the expected effect of a given increase in mutations A list of such conditions with their incidence in the population of Northern Ireland has been compiled by STEVENSON (U N Report 1958 pp 197—199) and is utilized here as a basis for the figures in Table 6 This table presents the development of an argument derived from the method originally devised by HALDANE (1932) for the estimation of the mutation frequency in traits with various modes of inheritance and recently applied by PENROSE (1956b) to this problem

The argument set forth in Table 6 results in two values *m* and *g* The first one *m* expresses the proportion of cases of the conditions listed taken as a whole which is due in each generation to fresh mutation The other value *g* expresses the contribution of genetic as opposed to environmental (including intra uterine) factors to the causation of such conditions It is evident that *m* also expresses the increase in incidence to be expected in the first filial generation (F_1) from the application of the D_2 it can be regarded as the reciprocal of the mean number of generations required for the elimination through loss of reproductive fitness, of noxious genes This interpretation springs from the principle underlying HALDANE s method the proportion of cases due to new mutation in a situation of genetic equilibrium is equal to the proportion of genes lost per generation As for *g* the genetic moiety in the production of the anomalies under study it must be noted that all of it is mutational in origin consisting as it does of mutant alleles which have been handed down

Table 6

Estimation of the mutational moiety in the production of certain prenatally determined conditions

1 Category (STEVENSON)	2 Birth incidence %	3 Genetic portion g	4 2 × 3	5 Estimated loss of reproductive fitness 1—F	6 Proportion* of cases due to new mutation per generation m	7 2 × 6
I Diseases and defects having an undisputed genetic aetiology						
Dominant	0.95	1.0	0.95	0.46**	0.46	0.437
Sex linked	0.04	1.0	0.04	0.5	0.17	0.007
Recessive	0.12	1.0	0.12	—	0.01	0.001
II Overt congenital malformations	0.98	0.72**	0.71	0.55**	0.34**	0.333
III A Some recessives with high gene frequency	0.09	1.0	0.09	—	0.01	0.001
III B See***	—	—	—	—	—	—
Mongolism	0.20	1.0	0.20	1.0	1.0	0.200
	2.38		2.11			0.979

Mean values $= \frac{2.11}{2.38} = 0.89$ $\qquad m = \frac{0.979}{2.38} = 0.41$ $\qquad g/m = 2.2$

* After PENROSE (1956 MRC Report, p. 190). For a dominant $m = 1 - F$. For a sex linked $m = (1 - F)/3$. For a recessive m = twice the gene frequency of each trait, and is taken here as 0.01 from one example given by PENROSE; a slight effect of consanguinity can also be neglected in this simplification, since the total effect of recessives on the mean value of m is seen to be small.

** Estimates derived from an analysis of various epidemiological data on congenital disease, to be presented elsewhere.

*** Traits with late expression and great dependance on post natal environmental factors; since the genetic mechanisms are mostly hypothetical, such traits are omitted here.

ageing on the offspring's sex ratio in a large human population to that observed after massive therapeutic irradiation, in the light of the hypothesis that both effects are mutational. Other figures are derived from irradiation of human somatic cells with effects which may be likened to mutation, i.e. to chromosomal changes which are transmitted to daughter cells when irradiated cells are called upon to reproduce themselves by mitosis. This "somatic mutation" concept of the leukaemogenic or carcinogenic effect of radiation, suggested prophetically by MULLER in 1927, has recently found a striking confirmation in the discovery of a chromosomal aberration in the bone marrow cells of leukaemic patients.

A provisional estimate for D of 30 r (gonad dose for 30 years, the average length of a human generation) is accepted as a working hypothesis in the U.N. Report (1958). It is obvious from Table 5 that estimates applicable to man vary widely, and it is reasonable to expect this figure to be different for various kinds of mutations. In any case, the geometric mean of the range

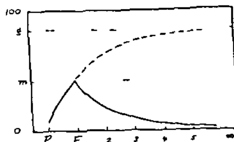


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Mean values $g = \frac{2.11}{2.38} = 0.89$ $m = \frac{0.979}{2.38} = 0.41$ $g\,m =$ [illegible]

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Table 7

The empirical approach to human risks using the atomic bomb data

A Estimation of the mean dose (calculated from the ABCC Report one parent exposure only)

Exposure category	*Relative number of births*	*Estimated mean dose*	*Product*
3	0.62	75 r	46.5 r
4 5	0.38	250	95.0
	1.00		141.5 r
2 (serving as control)		7.5	7.5
Difference (additional exposure to heavily exposed group)		surface dose	134.0
Portion reaching the gonad (1/2)			67 r

B Calculation of D_2 from the Hiroshima Nagasaki data

Incidence of major malformation at birth (from Table 2 Part I of present paper) father exposure only

In control group (light exposure) 0.7629

In offspring of heavily exposed 1.3110

Increase induced by 67 r (1.3110—0.7629)/0.7629 = 0.716

Increase induced by 1 r 0.716/67 = 0.0107

The increase induced by 1 r in the $F_1 = m/D_2$ (see text) the value of m for congenital malformations is 0.34 (Table 6)

Then $D_2 = 0.34/0.0107 = 31.8$ r

ment are in dispute (FRASER 1959 NEEL 1958) is based on an analysis of various epidemiological data on such anomalies, to be presented in another publication

If one accepts the values given above for D_2 (30 r) and in Table 6 for m (0.41) and g (0.89), it is possible to establish a coefficient of increase of the risk toward the conditions discussed above from irradiation of the human gonad before the end of the fertile period equal to $m/D_2 = + 0.014$ per roentgen in the F_1 and $g/D_2 = + 0.03$ per roentgen in the entire posterity including the F_1 ($F_1 \to \infty$) Hence one estimates that the present load of radiation to the gonads from the diagnostic use of roentgen rays (4.5 r per 30 years in North America Nat Acad Sci 1956) has already caused an increase, which is rising from 6.3 % to 13.5 % per generation, in the incidence of prenatally determined disease

2 *The empirical approach*

Whatever may be the real values of the parameters D_2 m and g the uncertainties which they raise may be circumvented by taking a direct approach to the data gathered in Japan as presented in Part I Father exposure alone shall be considered here in order to remove the doubt springing from the possibility of somatic (i e extra genetic) effects in exposed mothers The loss through malformation apparently induced in the father heavily exposed group of births (Table 7 B) is seen to represent 71.6 % of the loss occurring in the light exposure group serving as a control It is recalled that the total genetic

for a greater or lesser number of generations, a portion of these, equal to m, comes from the first parental generation

According, then, to this theoretical model, illustrated in Fig 5, the presumed total effect in the posterity ($\Gamma_1 \rightarrow \infty$) of the application of D_t to one parental generation is an increase, g, in the incidence of the conditions under study, of which m would occur in the Γ_1 Should the increased mutation producing load D be applied permanently to all succeeding generations, the expected increase would rise from m per filial generation and tend, at equilibrium, to reach g for each generation The rate of rise would be greatest in the early generations (PENROSE, see MRC Report, pp 190—195)

The argument leading to the determination of m and g (Table 6) admittedly has grave limitations *the main ones of which are as follows*

1 The value of m is seen to depend mainly on the value for the average loss of reproductive fitness in individuals with dominant conditions This loss of fitness is not known with any precision for more than a very few conditions, one hopes that the study initiated by NEWCOMBE (1957) on electronically analyzed vital statistics may soon fill gaps in information here The values given (column 5 of Table 6) are based on a review, to be presented elsewhere, of a number of prenatally determined conditions The values adopted are conservative, and almost certainly too low, inasmuch as probable slight losses of reproductive fitness, through reduced eligibility for mating, have been ignored

2 The value of m based on 'dominant traits of STEVENSON s category I would be too high if an appreciable proportion of such cases were phenocopies, that is, due to the action of hypothetical post conceptional environmental factors leading to an effect similar to that produced in other cases by mutant genes Such occurrences cannot be excluded a priori, but to our awareness the only example of such a situation to have been convincingly documented is that of retinoblastoma (VOGEL 1957)

3 As pointed out in the U N Report, Stevenson's definition of a recessive factor is very strict For many traits, there is partial dominance the expression of an abnormal allele in the heterozygous is present but slighter, or less readily detected, than in the homozygous This has the effect of overestimating the number of cases due to new mutation if such a factor has been classed as a dominant, most conditions showing this phenomenon to a marked degree, however, are listed in Stevenson s category II to be discussed presently The expected overestimation of m due to these reasons cannot be measured, perhaps it compensates for the underestimation alluded to in (1)

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In control group (light exposure) 0 7629

In offspring of heavily-exposed 1 3110

Increase induced by 67 r (1 3110—0 7629) 0 7629 = 0 716

Increase induced by 1 r 0 716/67 = 0 0107

The increase induced by 1 r in the $F_1 = m/D_2$ (see text) the value of m for congenital malformations is 0 34 (Table 6)

Then D_2 = 0 34 0 0107 = 31 8 r

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review (see Part I) shows that within the limitations in time and in method, of the genetic survey a new analysis of the data based on the separate study of the exposure of each parent alone brings out definite indications of genetic ill effects of atomic radiations at a high level of statistical significance

A review of the sources of increased radiation to which man has been subjecting himself through his own efforts shows that the hazard from the diagnostic use of roentgen rays is much greater than comes from the radio-nuclides of bomb test fall out Medical practices with respect to roentgen rays present a definite hazard moderate in degree, to future generations which it is the onus of to day s physicians to minimize One may estimate with a fair degree of confidence that the incidence of inborn defects and diseases in children born at this time in technologically advanced countries includes a contribution of 6 to 13 % by mutations induced prior to conception through the diagnostic use of roentgen rays Part of the risk of course is inevitable in the interest of sound medical practice the benefits afforded the human race through the proper health guarding use of ionizing radiation compensates well for the expected genetic ill effects

Important though the risks from the civilized use of radiation may be they would become insignificant in comparison to the total genetic harm due to fall out from nuclear devices exploded over populated areas The duty that springs from knowledge obliges the physician to impart this knowledge even if incomplete to his colleagues and to the public It is misleading and unwarranted to make statements on the inexistence or the insignificance of a genetic hazard of radiation to man

Acknowledgement

I am grateful for valuable assistance and encouragement to Professor D J Conway of the Department of Paediatrics Professor E O Dodson of the Department of Biology and Doctor A C Smith formerly of the Department of Mathematics all of the University of Ottawa I also thank Miss M Gauthier for her patient secretarial help

SUMMARY

From various experimental and clinical data on the incidence and the genetic portion of congenital anomalies and on their induction by ionizing radiation an attempt has been made to predict the magnitude of the increase in human reproductive wastage in the first generation which would lie in the neighbourhood of + 0 01 per roentgen (gonad dose) This estimate agrees roughly with the empirical coefficient brought out by the analysis of observations made in Japan on the genetic effect of atomic bombs The implications of this parameter are discussed in connexion with the risks to which human populations are or may be exposed through clinical use of roentgen rays fall-out from nuclear weapon tests and the possible use of such weapons in warfare

ZUSAMMENFASSUNG

Auf Grund des Studiums verschiedene experimentelle und klinische Daten uber die Haufigkeit und den genetischen Anzahl kongenitaler Anomalien sowie deren Induktion durch

effect has been shown to be significant, the main limitation to confidence here is the estimated amount of radiation This is taken (Table 7 A) to be a gonad dose 67 r greater in the heavy exposure group than in the light one, the assumption being made that one half of the skin dose reached the gonad In this connexion, it is noted that in the U N Report, a factor of one third is employed, which would tend, naturally, to increase the expected risk from radiation

If the additional dose received by the gonads of heavily irradiated fathers can validly be taken as 67 r, one calculates a coefficient of increase of the severely malformed births per roentgen in the F_1 of + 0 0107, a figure which lies satisfactorily close to that of + 0 014 derived above This agreement points to the validity of the theoretical model and calculations presented in the first part of this discussion *On the basis of these, the total loss induced in the* posterity of irradiated individuals would be g/m = 2 2 times as great as that observed in the F_1 This cannot be verified, the genetic study in Hiroshima and Nagasaki having been terminated

Another check of the coefficient given in the preceding paragraph against the theoretical model consists in deriving the value of D , this is shown in Table 7, B The value of 31 8 r thus obtained from a consideration of induced malformations (the value of m applicable to the remainder of the reproductive loss being unknown) is in close enough agreement with the provisional estimate D_2 = 30 r (U N Report 1958) to suggest that no greater effect than has been shown could have emerged from the atomic bomb genetic study

The loss induced in Hiroshima and Nagasaki (observed increase of 77 5 % in total reproductive wastage in the F_1 expected additional increase of 93 % *in the ensemble of subsequent generations)* in the progeny of severely irradiated individuals may be used to predict the order of magnitude of the genetic effects of thermonuclear weapons much more powerful than the uranium bombs detonated in Japan, since only the survivors, i e those receiving *not more* than 500 to 600 r (total body surface dose), could procreate But the total genetic ill effect per detonation, affecting a population occupying a much wider area than the range of the bombs of 1945, would be immeasurably greater than that recorded in Hiroshima and Nagasaki In the case of a thermonuclear weapon detonated over a large city, it is not unreasonable to expect a near two fold increase in the incidence of reproductive wastage and prenatally determined disease in the posterity of a million people or more

Conclusions

Although the report of the survey conducted by the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki has been widely quoted as failing to detect any consistent genetic effects of exposure to the bombs, the present

review (see Part I) shows that within the limitations in time and in method of the genetic survey, a new analysis of the data based on the separate study of the exposure of each parent alone brings out definite indications of genetic ill effects of atomic radiations at a high level of statistical significance

A review of the sources of increased radiation to which man has been subjecting himself through his own efforts shows that the hazard from the diagnostic use of roentgen rays is much greater than comes from the radio-nuclides of bomb test fall out Medical practices with respect to roentgen rays present a definite hazard moderate in degree to future generations which it is the onus of to day s physicians to minimize One may estimate with a fair degree of confidence that the incidence of inborn defects and diseases in children born at this time in technologically advanced countries includes a contribution of 6 to 13 % by mutations induced prior to conception through the diagnostic use of roentgen rays Part of the risk of cour e is inevitable in the interest of sound medical practice the benefits afforded the human race through the proper health guarding use of ionizing radiation compensates well for the expected genetic ill effects

Important though the risks from the civilized use of radiation may be they would become insignificant in comparison to the total genetic harm due to fall out from nuclear devices exploded over populated areas The duty that springs from knowledge obliges the physician to impart this knowledge even if incomplete to his colleagues and to the public It is misleading and unwarranted to make statements on the inexistence or the insignificance, of a genetic hazard of radiation to man

Acknowledgement

I am grateful for valuable assistance and encouragement to Professor D J Conway of the Department of Paediatrics Professor E O Dodson of the Department of Biology and Doctor A C Smith formerly of the Department of Mathematics all of the University of Ottawa I also thank Miss M Gauthier for her patient secretarial help

SUMMARY

From var ous experimental and clinical data on the incidence and the genetic portion of ongenital anomalies and on their induction by ionizing radiation an attempt has been made to predict the nagnitude of the increase in human reproductive wastage in the first genera ion which would be in the neighbourhood of + 0 01 per roentgen (gonad dose) This esti mate agrees roughly with the empirical coefficient brought out by the analysis of observations made in Japan on the genetic effect of atomi bombs The implications of this parameter are discussed in connexion with the risks to which human populations are or may be exposed through clinical use of roentgen rays fall-out from nuclear weapon tests and the possible use of such weapons in warfare

ZUSAMMENFASSUNG

Auf Grund des Stud ums verschiedene experimentelle und klinische Daten uber die Haufig keit und den geneti chen Anzahl kongenitaler Anomalien sowie deren Induktion durch

effect has been shown to be significant, the main limitation to confidence here is the estimated amount of radiation This is taken (Table 7 A) to be a gonad dose 67 r greater in the heavy exposure group than in the light one, the assumption being made that one half of the skin dose reached the gonad In this connexion, it is noted that in the U N Report, a factor of one third is employed, which would tend, naturally, to increase the expected risk from radiation

If the additional dose received by the gonads of heavily irradiated fathers can validly be taken as 67 r, one calculates a coefficient of increase of the severely malformed births per roentgen in the F_1 of + 0 0107, a figure which lies satisfactorily close to that of + 0 014 derived above This agreement points to the validity of the theoretical model and calculations presented in the first part of this discussion On the basis of these, the total loss induced in the posterity of irradiated individuals would be $g/m = 2.2$ times as great as that observed in the F_1 This cannot be verified, the genetic study in Hiroshima and Nagasaki having been terminated

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BOOK REVIEWS

THE BASIC PHYSICS OF RADIATION THERAPY By Joseph Selman 671 pages 246 illustrations and 70 tables Charles C Thomas, Springfield 1960 Price $ 14 50

This book according to the preface is intended particularly for trainee radiologists and technicians but also as a refresher course for practicing radiologists As very little previous knowledge is presupposed in most readers an introductory chapter covers a little elementary mathematics The following chapters concern the structure of matter and the nature of radiation reaction between radiation and matter generation of roentgen rays roentgen apparatus the measurement of quantity and quality of roentgen and gamma rays practical roentgen dosimetry as well as dose planning in radiotherapy and various accessories for beam directioning

Subjects treated in the other chapters include radioactivity and nuclear physics supervoltage apparatus radium and radon therapy and the use of radioisotopes in therapy and diagnosis The final two chapters deal with radiobiology and radiation protection

The text is characterized by verbosity and there are numerous repetitions This may be an advantage from the point of view of teaching but it inevitably leads to the book having much less real content than would be expected from its size The author states that his aim is to 'explain the fundamental physical principles underlying radiation therapy in as comprehensive and comprehensible way as possible without sacrificing accuracy for simplicity but it appears to the reviewer that he has not entirely succeeded in the latter part of his objective There are many loose and misleading expressions and indeed many factual errors perhaps the worst is on p 589 where radiation doses to different parts of a body are added together to produce a total body dose This procedure (which of course ould have been correct if it had been a matter of *integral* doses) is almost comparable to taking m ith and rectal temperatures separately and adding them to give a total body temperature of about 74 C The explanation of the various dose concepts and units is in many places defecti e and no clear distinction is made between intensity and dose rate The genetic effects of radiation are mentioned only very briefly in the last chapters

These and a great number of similar shortcomings make the book unsuitable as a self tuition manual for the tiro and the experienced reader will probably find the going unnecessarily heavy

S en Benner

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Radiation doses and protection are important subjects in dental radiography but appropriate information is lacking in these fields This book unfortunately contains so many errors on the elementary level that it can hardly be recommended as a contribution towards extending knowledge

Lars Eric Larsson

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INVESTIGATION OF THE DISTENSION CAPACITY OF THE HUMAN GALLBLADDER

by

ERIC GUNNARSON

The emptying capacity of the gallbladder during cholecystography has received much attention. The gallbladder is however not only capable of emptying, i.e. decreasing in volume, but may also distend, i.e. increase in volume.

TATERKA (1930) found that the gallbladder expanded during cholecystography after the intravenous injection of decholin, a bovine bile preparation with a choleretic effect. HULTÉN (1943) described a case in which ingestion of a fatty meal was followed not by a decrease but by an increase in the volume of the gallbladder. The capacity of the gallbladder to expand has not, however, been studied systematically during cholecystography. This paper is concerned with the capacity of the gallbladder to expand in health and in disease.

Material. The distension of the gallbladder was studied by cholecystography in 300 cases. Good concentration power and absence of stones were evident in 133 cases; of these subjects 60 were volunteers who had never had abdominal pain and 73 had had pain suggestive of biliary disease.

Biliary disease was demonstrable at cholecystography in the remaining 167 cases. In 99 of these good filling of the gallbladder was obtained via the cystic

Submitted for publication 21 January 1961. From the Roentgendiagnostic Department (Director Prof. Olle Olsson), University Hospital, Lund, Sweden.

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The text is characterized by verbosity and there are numerous repetitions. This may be an advantage from the point of view of teaching, but it inevitably leads to the book having much less real content than would be expected from its size. The author states that his aim is to explain the fundamental physical principles underlying radiation therapy in as comprehensive and comprehensible way as possible without sacrificing accuracy for simplicity, but it appears to the reviewer that he has not entirely succeeded in the latter part of his objective. There are many loose and misleading expressions and indeed many factual errors, perhaps the worst is on p. 589, where radiation doses to different parts of a body are added together to produce a total body dose. This procedure (which of course would have been correct if it had been a matter of *integral* doses) is almost comparable to taking mouth and rectal temperatures separately and adding them to give a total body temperature of about 74° C. The explanation of the various dose concepts and units is in many places defective and no clear distinction is made between intensity and dose rate. The genetic effects of radiation are mentioned only very briefly in the last chapters.

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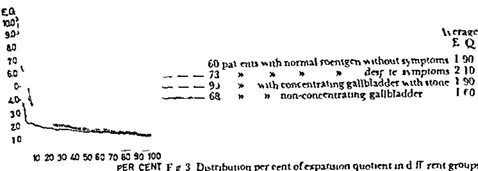


Fig 3 Distribution per cent of expansion quotient in different groups

morphine raised the pressure in the biliary tract by 150 to 250 mm water in cholecystectomy cases with an indwelling T tube We obtained similar results in a preliminary investigation with selective measurements of the pressure following cholecystectomy without leakage of contrast medium along the T tube at postoperative cholangiography

The size of the gallbladder was measured during cholecystography, morphine (0 05 mg/kg bodyweight) was injected subcutaneously and at the same time 20 ml Biligrafin forte were injected intravenously Two hours later comparable views were obtained of the contrast filled gallbladder

Measurement of expansion of gallbladder The contrast filled gallbladder was measured planigraphically before and after the injection of Biligrafin and morphine The ratio between the volume after expansion and before expansion, expansion quotient E Q may be obtained from the following formula The ratio of volumes =

$$\left(\sqrt{\frac{\text{Surface area during expansion}}{\text{Surface area during cholecystography}}}\right)$$

A gallbladder of high contrast density may appear larger than one of the same size but of lower density In a given case however the contrast density is the same before as after expansion and the expansion quotient is given as a ratio

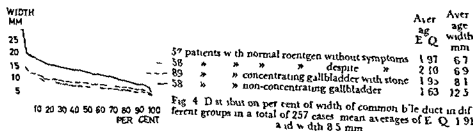


Fig 4 Distribution per cent of width of common bile duct in different groups in a total of 257 cases mean averages of E Q 1 91 and width 8 5 mm

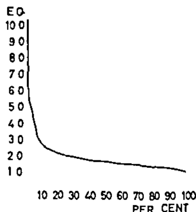


Fig 1 Expansion quotient of the gallbladder Distribution per cent in 300 cases according to degree of expansion Average E Q 1 86

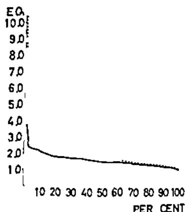


Fig 2 Expansion quotient of concentrating (232 cases average E Q 2 01) and non concentrating gallbladders (—— 68 cases average E Q 1 60)

duct and the concentration power was normal, in 68 the concentration power was poor or absent Thirty two cases in which no filling of the gallbladder was obtained at the first examination were subsequently examined by intravenous cholegraphy

Method Cholecystography was carried out with the sodium salt of iopanoic acid (PETERHOF 1956) All examinations included films with the patient supine, in addition, in some cases in which the density of the contrast medium was high, frontal and lateral views were obtained with the patient erect Repeated examinations of the same patient with the same contrast medium and with comparable projections showed that the size of the gallbladder is fairly constant

Choleresis was induced in order to bring about an expansion of the gallbladder, and attempts were made to prevent the flow of bile through the papilla of Vater Choleresis was produced by injection of Biligrafin forte which, in the dog in a dose of 200 mg/kg bodyweight, will double the flow of bile for more than 2 hours (HORNYKIEWYTSCH 1956)

Biligrafin also produces choleresis in human beings This effect was studied in association with postoperative cholangiography The passage of bile to the intestine was retarded or inhibited by the injection of morphine (0 05 mg/kg bodyweight) in 14 subjects who had undergone cholecystectomy and had had a T-tube inserted The flow of bile from the T tube was measured at periods of 10 min before and after the intravenous injection of Biligrafin The rate of flow was greatest 50 min after the injection and increased on the average by 70 % (from 3 to 5 2 ml), and always more than 40 % REACH (1913) showed that morphine retarded or stopped the flow through the common bile duct McGOWAN, BUTSCH & WALTERS (1936) found that an injection of 1 cg of



Fig 6 Case with symptoms of biliary disease a) Normal cholecystography b) Considerable widening after injection of Biligrafin and morphine Normal common bile duct

(20 %) the expansion was only slight, the average for the entire material was 1 86 or about twofold

The expansion quotient of filled and unfilled gallbladders is shown in Fig 2 In the 232 cases in which the gallbladder was filled there was a twofold increase (E Q = 2 01) and in one third of the cases it was more marked (E Q = 3) In the 68 cases in which the gallbladder was not filled the average value was smaller (E Q = 1 6) and only in 9 cases (13 %) was there any considerable expansion (E Q = 2 40)

The expansion quotient in different groups is given in Fig 3 The values in cases with normal findings at cholecystography (133) were the same as for the entire material with a gallbladder capable of concentrating contrast medium (232) Of these 133 cases those with biliary symptoms (73) showed a higher degree of expansion (E Q = 2 10) than cases without symptoms (E Q = 1 90) In cases with stone but in which the gallbladder nevertheless filled (99) the degree of expansion was the same (1 90) as in normal cases without symptoms Of the 68 cases in which the gallbladder did not fill the average expansion quotient was as was mentioned, less and only in a few was it high

Width of the common bile duct and the expansion quotient Cases which have been subjected to cholecystectomy and which have postoperative symptoms often



Fig 5 Normal cholecystography a) Contrast medium in common bile duct b) 2 hrs after injection of Biligrafin and morphine distension of gallbladder

Significance of projection It was mentioned that in some cases (these totalled 51) of high contrast density, frontal and lateral views were obtained with the patient erect It was generally found that the ratio of expansion did not vary with posture (Fig 7) It is only in the supine posture that normally the gall bladder is filled completely with contrast medium, for bile containing contrast medium has a relatively high specific gravity, and the neck of the gallbladder and the cystic duct run dorsally to the common bile duct furthermore, the heavier bile overflows into the common bile duct in this position (Fig 5)

In 20 of the 51 cases it was possible to measure the width of the common bile duct with the patient supine and erect This examination was performed to determine that the contrast medium was uniformly distributed and that no layer formation, which would affect the width of the common bile duct, had occurred when the patient was placed in the supine position There was no evidence of any appreciable degree of layer formation between the bile mixed with contrast medium and the ordinary bile in the common bile duct (Fig 10)

Expansion quotient of the gallbladder The expansion quotient of the gallbladder varies widely (Fig 1) In 80 cases (28 %) the volume of the gallbladder marked ly increased after the injection of Biligrafin and morphine but in 60 cases

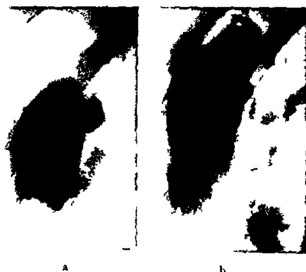


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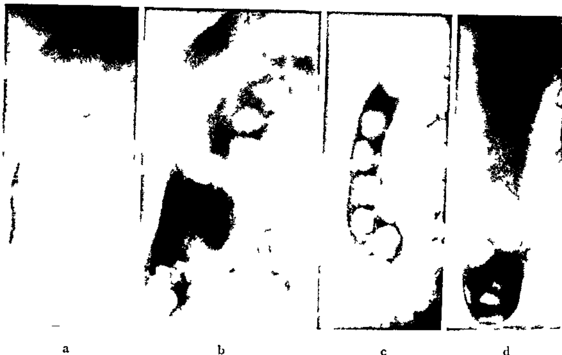


Fig 7 Case with mild biliary symptoms a) Supine Stone in well filled gallbladder b) Marked expansion quotient c) and d) Erect Expansion quotient unaltered

show considerable widening of the biliary ducts after the injection of morphine during cholegraphy (GUNNARSON 1956)

In 257 of the present 300 cases it was possible to measure not only the expansion quotient of the gallbladder but also the width of the common bile duct and in some cases the widths of the hepatic duct and the right and left hepatic ducts were also determined As to the width of the common bile duct (given in Fig 4) an opposite tendency as compared with the gallbladder was noted, in the 58 cases of non concentrating gallbladders, with a low expansion quotient (1 63), the common bile duct was usually wide (average 12 5 mm), in the 89 cases of stone in which the gallbladder filled and in which there was a high average degree of expansion (E Q = 1 95) the width was usually less (8 1 mm), in normal cases with and without biliary symptoms the width of the common bile duct was about the same (6 9 and 6 7) The mean for the entire material was 8 5

Discussion

The gallbladder has two main normal functions, one being to concentrate and serve as a reservoir for the bile, which plays an important role in the metabolism of fat Concentrated bile, in addition to its digestive action, also possesses a bacteriostatic quality The reason why fair amounts of liver bile flow through the narrow and tortuous cystic duct instead of through the

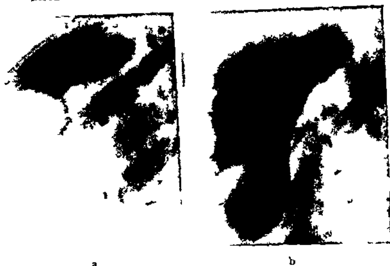


Fig 8 Case with chron c b liary symptoms a) Cholecystography good concentration of contrast med u n st ne present b) After B l grafin and morphine ma ked expan ion of gallbladder Co nmon bile duct of normal width

wider common bile duct is because the latter can be shut off by the sphincter of Oddi This occurs during fasting The capacity of the gallbladder as a depot depends on the amount it can contain and its power of concentration

The gallbladder also serves as a regulator of the intrabiliary pressure This function was not realized until a few decades ago (POTTER & MANN 1926, IVY & SANDBLOM 1934 GERTZ 1946 EKDAHL 1953) It was the clinical observation that certain patients without mechanical causes such as stone or stricture of the common bile duct had biliary and intestinal symptoms after cholecystec tomy that finally lead to the discovery of this function

The concentrating power of the gallbladder has received much attention in considerations of biliary disease It might be mentioned that GERTZ found postoperative symptoms after cholecystectomy in 27 % of patients in whom contrast filling of the gallbladder was obtained at preoperative cholecystography but in only 11 % of those in whom no such filling was obtained The difference reported by EKDAHL was still more striking, 54 % and 7 % respectively

The importance of the gallbladder in a given case as a reservoir and as a pressure regulator depends on its capacity to concentrate and to expand The latter quality may be deduced from the expansion quotient The correlation between the concentrating power of the gallbladder and the expansion quotient is shown in Figs 2 and 3 It is clear from these figures that even in the presence of stones the gallbladder may still be able to expand if it can concentrate bile Any decrease in the concentrating power is accompanied by a decrease in the expansion capacity i e there is an approximate relationship between the con



Fig 9a



Fig 9b



Fig 10a



Fig 10b

Fig 9 Case with chronic biliary symptoms At cholecystography no contrast medium in the gallbladder a) 50 min after Biligrafin moderate filling stone present b) 2 hrs after morphine slight distension of gallbladder width of common hepatic duct considerably increased

Fig 10 Case with chronic biliary symptoms a) Intravenous cholegraphy with morphine supine moderate amount of contrast medium in common bile duct containing numerous stones b) Erect width of common bile duct unchanged but stones have now gravitated downwards

centrating power and the expansion quotient Observations made in the present investigation suggest, however, that in the evaluation of a given case the expansion capacity is to be preferred Postoperative intestinal and biliary symptoms were found to be much more common after the removal of gallbladders which had filled at cholecystography than in those which had not filled It is clear from Fig 4 that the width of the common bile duct in cases in which the gallbladder did not fill and with a low expansion quotient was almost twice that found in cases in which the gallbladder showed concentrating power and marked expansion *This suggests that the volume of the bile ducts increases and thereby,* at least partly, compensates for the loss of function of the gallbladder as a reservoir and pressure regulator

SUMMARY

The expansion quotient of the gallbladder was studied during cholecystography with choleresis by the injection of Biligrafin and closure of the spincter of Oddi by the injection of morphine The relationship between the concentrating power of the gallbladder and the expansion quotient as well as the width of the common bile duct was studied The results are discussed in relation to so called postoperative dyskinesia

ZUSAMMENFASSUNG

Es wurde der Expansionsquotient der Gallenblase während Cholecystographie und Cholerese mittels Injektion von Biligrafin und die Schliessung des Sphincter Oddi mittels Morphin

injektion studiert Es wurden auch die Beziehungen zwischen dem Konzentrationsvermogen der Gallenblase und dem Expansionsquotienten wie auch die Weite des gemeinsamen Gallenganges untersucht Die Resultate werden in Bezug auf die sogenannte postoperative Dyskinesie besprochen

RÉSUMÉ

L auteur a etudié le quotient d expansion de la vésicule biliaire au cours de la cholécystographie avec cholérese par injection de Biligrafin et fermeture du sphincter d Oddi sous l effet d une injection de morphine Il a étudié les relations entre le pouvoir de concentration de la vésicule biliaire et le quotient d expansion et le calibre de la voie biliaire principale Il examine ces résultats en les rapprochant de ce qu on appelle dyskinésie post-operatoire

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Fig 9a

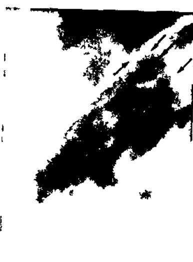


Fig 9b



Fig 10a

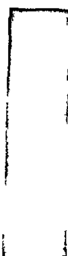


Fig 10b

Fig 9 Case with chronic biliary symptoms At cholecystography no contrast medium in the gallbladder a) 50 *min after Biligrafin* moderate filling, stone present b) 2 hrs after morphine slight distension of gallbladder width of common hepatic duct considerably increased

Fig 10 Case with chronic biliary symptoms a) Intravenous cholegraphy with morphine supine moderate amount of contrast medium in common bile duct containing numerous stones b) Erect width of common bile duct unchanged but stones have now gravitated downward

centrating power and the expansion quotient Observations made in the present investigation suggest, however, that in the evaluation of a given case the expansion capacity is to be preferred Postoperative intestinal and biliary symptoms were found to be much more common after the removal of gallbladders which had filled at cholecystography than in those which had not filled It is clear from Fig 4 that the width of the common bile duct in cases in which the gall bladder did not fill and with a low expansion quotient was almost twice that found in cases in which the gallbladder showed concentrating power and marked expansion This suggests that the volume of the bile ducts increases and thereby, at least partly, compensates for the loss of function of the gallbladder as a reservoir and pressure regulator

SUMMARY

The expansion quotient of the gallbladder was studied during cholecystography with choleresis by the injection of Biligrafin and closure of the spincter of Oddi by the injection of morphine The relationship between the concentrating power of the gallbladder and the expansion quotient as well as the width of the common bile duct was studied The results are discussed in relation to so called postoperative dyskinesia

ZUSAMMENFASSUNG

Es wurde der Expansionsquotient der Gallenblase wahrend Cholecystographie und Cholerese mittels Injektion von Biligrafin und die Schliessung des Sphincter Oddi mittels Morphin

injektion studiert Es wurden auch die Beziehungen zwischen dem Konzentrationsvermogen der Gallenblase und dem Expansionsquotienten wie auch die Weite des gemeinsamen Gallenganges untersucht Die Resultate werden in Bezug auf die sogenannte postoperative Dyskinesie besprochen

RÉSUMÉ

L auteur a étudié le quotient d expansion de la vésicule biliaire au cours de la cholécystographie avec cholérèse par injection de Biligrafin et fermeture du sphincter d Oddi sous l effet d une injection de morphine Il a étudié les relations entre le pouvoir de concentration de la vésicule biliaire et le quotient d expansion et le calibre de la voie biliaire principale Il examine ces resultats en les rapprochant de ce qu on appelle dyskinésie post-opératoire

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT B (DIRECTOR DOCENT N P G EDLING), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

ALUMINIUM PNEUMOCONIOSIS

A roentgendiagnostic study of five cases

by

NILS P G EDLING

The effect on the lungs of aluminium inhaled as a fine powder in large quantities has been a subject of conflicting opinions No clinical or radiologic evidence has been produced in examinations of aluminium workers in Great Britain and the United States, whereas German investigators during World War II reported on a number of aluminium workers displaying roentgen changes indicating pulmonary fibrosis During the stamping of powdered aluminium in the United States the powder is coated with a thin film of stearine this gives rise only to foreign body reactions and does not cause pulmonary fibrosis Stearine was unobtainable in Germany during the war and a paraffin substance was used in its place The paraffin and not the aluminium has been held responsible for the lung fibrosis (SHANKS and KERLEY 1950) It is probable, instead, that the paraffin layer might have been defective and not capable of protecting the alveolar tissue from the particles of metal

CAMPBELL et coll (1957), in a review of observations and reports of many investigators on the effects of aluminium on human subjects, stated that the inhalation of aluminium or its oxide or hydrate, does not injure the pulmonary system According to this view, no true aluminosis of the lungs should

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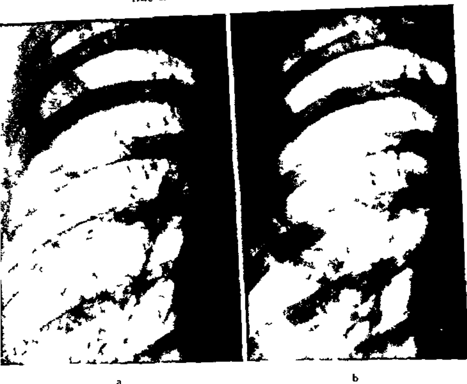


Fig. 1. Case 1. Aluminium pneumoconiosis. a) 1950. Extensive fine linear pattern and small nodules with small patchy densities in upper lobe. b) 1953. Only a fine linear pattern persists. No pulmonary contracture.

exist. Other studies, however (GORALEWSKI 1950, SCHINZ, BAENSCH, FRIEDL, UEHLINGER 1952, LEDERER 1953, FORSSMAN et coll. 1961), seem to have established that the inhalation of aluminium dust may produce fibrosis.

Roentgenologic features observed in five patients long exposed to air containing aluminium dust form the subject of this paper; these five cases are the only ones with lung changes in aluminium workers reported in Sweden. All the clinical indications of aluminium dust pneumoconiosis were present (FORSSMAN et coll. 1961).

Material. The 5 patients belonged to a group of about 35 factory operatives who during a certain period of their lives were engaged without protection in stamping of powdered aluminium. The aluminium scrap used was of a high degree of purity, and the air contained a very considerable amount of dust. These operatives at the end of a working day looked like metal statues.

Random tests made with filter papers and impingers showed that the aver

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Fig 2 Case 2 Aluminium pneumoconiosis 1950 Extensive linear pattern and small nodules with a few areas of hazy opacity mainly in the apical and middle zones Hila and trachea slightly displaced

age dust content varied between 4 to 50 mg/m³, and was sometimes much higher, most of the particles were smaller than 4 μ (FORSSMAN et coll 1961)

After four of the patients had been exposed to the aluminium dust for periods ranging from 2 to 4 years and the remaining one for 13 years, they developed symptoms mainly in the form of breathlessness The workers either left the factory or were given work that did not involve the inhalation of dust After some time three of them were entirely free from dyspnoea and regained full working capacity, the condition of the remaining two deteriorated and resulted in total disablement one died In the latter case post mortem examination revealed non specific inflammatory changes of a chronic character, with fibrosis and emphysema of the lungs

None of the patients had been exposed to dust containing free silica One of the patients was thought to have tuberculosis when he first developed chest symptoms, a diagnosis which was not confirmed by careful observation over a period of some months

Case reports

Case 1 Male aged 60 According to reports a roentgen examination of the lungs in 1946 had shown no abnormalities In 1950 extensive fine striations and minute nodular opacities were observed in both lungs and patchy densities in the upper lobes (Fig 1a) No hilar or pleural changes Repeat lung examinations from 1950 to 1960 showed that the changes had diminished (Fig 1b) and that only a moderate amount of fine striations persisted There was no evidence of pulmonary contracture

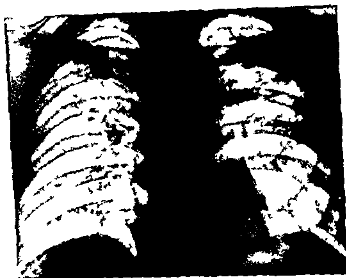


Fig 3 Case (same as in fig 2) 1953 Coarse linear pattern and patchy areas of opacity in apical zones Basal emphysema Increased pulmonary contracture Small pleural adhesions

Case 2 Male aged 35 Roentgen examinations of the lungs carried out in 1949 had shown extensive small nodular opacities in the apical zones of both lungs and patchy densities in the apical zone of the right lung Roentgen examination a year later (Fig 2) revealed that the middle zones and to some extent the lower zones had become involved The hila were displaced slightly upwards and backwards and the trachea to the right indicating some degree of pulmonary contracture Small pleural adhesions to the diaphragm were present An examination performed in 1953 (Fig 3) showed that the nodules had almost disappeared but there were coarse striations and patchy densities in the upper zones the contracture had increased There was evidence of emphysema at the bases The contracture and emphysema increased only slightly from 1953 to 1960

Case 3 Male aged 45 Roentgen examination of the lungs in 1947 had shown small nodules in the lungs which at an examination in 1948 had progressed to wide striations with contracture of the lungs An examination two years later revealed extensive striation and moderate contracture mainly posteriorly in the upper zones with displacement of the hila upwards and the trachea to the right Emphysema and some opacities were present in the basal zones and small pleural adhesions at the left diaphragm Repeat examinations during the next ten years showed slightly increased contracture of the lungs

Case 4 Male aged 48 Roentgen examinations of the lungs carried out in 1946 had shown extensive striations and patchy rounded opacities some of a miliary type and emphysema a year later the rounded opacities were no longer visible A roentgen examination three years after that (Fig 4) revealed extensive patchy rounded densities and striations in the upper and middle zones with displacement of the hila upwards and backwards and of the trachea to the right The lower zones were slightly *affected* *Basal* emphysema was present and the pleura was thickened at the mediastinum and diaphragm The findings were unchanged during the next three years



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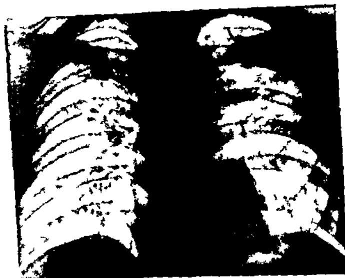


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a b

Fig 4 Case 4 Aluminium pneumoconiosis Extensive linear pattern in apical and middle zones with some involvement of basal zones evidence of emphysema in latter regions Displacement of hila Pleural adhesions Diaphragm flattened

Case 5 Male aged 64 According to reports a few calcifications were visible in the lungs in 1946 but there were no other changes Roentgen examination in the following year (Fig 5) revealed fine and coarse striations mainly posteriorly in the upper zones with incipient pulmonary contracture The diaphragm was flattened on the left side the pleura was thickened Three years later (Fig 6) the opacities in the upper zones and the contracture had increased with displacement of the hila There were some striations in the basal zones and evidence of marked emphysema At repeat lung examinations from then to 1960 the parenchymal changes the contracture and the emphysema had further increased The trachea was displaced and there were now extensive pleural adhesions (Fig 7)

Comments All five cases presented evidence of fine striations or nodular rounded opacities In four of the cases coarse striations and pulmonary contracture, as well as basal emphysema and thickening of the pleura had developed in from 1 to 2 years Further follow up examinations showed that in three cases the lung either remained unaltered or increased slightly and, in one case, markedly progressed The observation time was 3 years in one case, and 10 years in each of the remaining three cases In the fifth case the initial changes diminished and no pulmonary contracture occurred during an observation period of ten years It is noteworthy that this case had had the longest time of exposure to the irritant

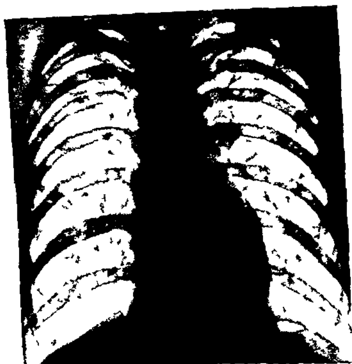


Fig 5 Case 5 Aluminium pneumoconiosis 1947 Fine and coarse linear pattern in upper zones basal emphysema Slight displacement of hila Diaphragm flattened

Discussion

Despite the doubts expressed regarding the existence of aluminium pneumoconiosis there seems to be no doubt of the clinical nature of the five cases under review These patients were the only ones affected out of a group consisting of some 35 operatives engaged in the same work this points to an individual disposition factor There was no case of pneumoconiosis in a parallel group of workers in the same factory which were occupied in manufacturing gold bronze and exposed to air that was just as dustladen

A striking feature in the roentgenologic follow up examinations of the lungs in four of the cases was the rapid development from initially fine striations or nodular densities to fibrosis with pulmonary contracture and thickening of the pleura This transition took place within a period of one or two years After the fibrosis had occurred further observations during a period of 10 years in three cases and of three years in one case revealed, with one exception no or only very slight progress In this latter case the changes developed into coarse striations and massive opacities which to some extent resembled the appearances in stage III of silicosis the pleural involvement also increased

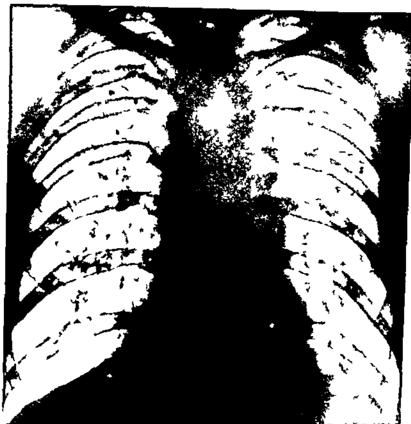


Fig 6 Case 5 (same case as in fig 5) 1950 Increase of the emphysema and contracture

In the fifth case the initial changes decreased and gave way to a moderate distribution of striations, no pulmonary contracture or emphysema was evident The findings in all the cases agree well with those summarized by WORTH and SCHILLER (1954) from the relevant literature, these authors maintain that the phenomena cannot be adequately separated into different stages as in silicosis

The roentgen findings in the five cases under review indicate in general a less fibroblastic activity in the lungs than that found in silicosis This did not seem to depend on less exposure to the irritant, as the quantity of aluminium dust was relatively great and the exposure time was long It was not possible to demonstrate the development of the initial changes into large nodules in any of the four progressive cases Moreover, even if fibrosis developed to a considerable extent, it was found subsequently to progress only in one case during the many years that the patients were kept under observation, however, despite the standstill during three years one of the patients died It is also noteworthy that in the different cases the roentgenologic aspects of the pulmonary contracture and emphysema were similar which indicates resemblance with observations made in cases of silicosis, in which the pulmonary



Fig 7 Case 5 (same case as in figs 5 and 6) 1960 Areas of massive opacity laterally in upper zones advanced emphysema of basal zones Pleural adhesions Marked pulmonary contracture with trachea displaced to the right

changes in workers subjected to the same type of exposure are characteristic (BRUCE & JONSSON 1943) In silicosis however there are greater variations in the densities from one case to another as well as in the progress of the disease The pleural involvement in two of the cases was fairly advanced

Despite the persistent fibrotic changes, two of the patients had no symptoms after the initial dyspnoea and were passed for insurance as fit for work In one of the cases the disease exhibited a regressive course with initial changes that diminished this never occurs in silicosis The working capacity of the patient was also unimpaired

The relatively mild course of the disease may be explained by the fact that aluminium particles when inhaled display a mechanism different from that of silica particles and exert a less stimulating effect upon the formation of fibrous tissue moreover they are resorbed and transported from the lungs fairly quickly This is supported by the postmortem examination of one of the cases in which only fibrosis and no aluminium was found

The features described are not sufficiently characteristic to be classed as diagnostic As in other types of pneumoconiosis the diagnosis is always difficult and must be based on the history together with roentgen findings reviewed in juxtaposition

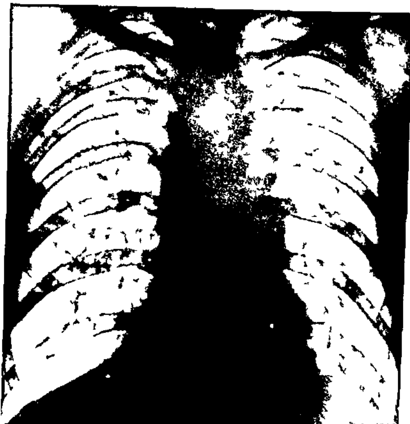


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FROM THE EDWARD MALLINCKRODT INSTITUTE OF RADIOLOGY (DIRECTOR PROF HUGH M WILSON) WASHINGTON UNIVERSITY SCHOOL OF MEDICINE ST LOUIS MISSOURI U S A

ANGIOGRAPHY OF MALIGNANT TUMORS IN MICE

by

ALEXANDER R MARGULIS ERIK CARLSSON and WILLIAM H McALISTER

Angiography is used extensively in the study and diagnosis of neoplasms (2 3 4 5 6 7 10 11 12 13 14 15) The correlation of the angiographic appearances with the histology of neoplasms has met with varied success WICKBOM was able to differentiate certain brain tumors by vascular studies (16) Dos SANTOS claimed that a characteristic arrangement of vessels constituted evidence of giant cell tumors of bone (5) and LINDGREN suggested that all tumors have more or less specific angiographic appearances (9) A typical arrangement of blood vessels for each neoplasm or groups of neoplasms is difficult to determine from available reports because of the small volume of the case material and lack of identical methods of study Even careful reports like those of LAGERGREN LINDBOM and SODERBERG (8) or BORELL FERNSTROM and WESTMAN (13) are based on only a few cases

Large numbers of tumors in various stages of growth are needed to establish whether characteristic appearances exist and if preliminary conclusions are to be reached within reasonable time experimental animals must be used Final conclusions will be reached in human material

Preliminary studies suggest that the degree of malignancy of neoplasms bears a relationship to the vascular configuration (Dos SANTOS LINDGREN, LAGERGREN inter al) (5 9 8) Greater knowledge of the significance of the

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SUMMARY

The roentgen appearances of the lungs in five workers exposed to aluminium dust are described and discussed Initial fine striations and nodular opacities followed by fibrosis with pulmonary contracture and emphysema and pleural changes were demonstrated The fibroblastic effect of aluminium on the lungs seems to be less active and more transient as compared to that of silica

ZUSAMMENFASSUNG

Das röntgenologische Aussehen der Lungen von 5 Arbeitern die Aluminiumstaub eingeatmet hatten wird beschrieben und diskutiert Initiale feine Streifigkeit und nodöse Verdichtungen denen eine Fibrose mit Lungenschrumpfung Emphysem und pleuralen Veränderungen folgte werden demonstriert Die fibroblastische Wirkung des Aluminiums auf die Lungen scheint weniger aktiv und vorübergehender zu sein als die des Quarzes

RÉSUMÉ

L auteur décrit l aspect radiologique des poumons de cinq ouvriers exposés à la poussière d aluminium Il a constaté au début de fines striations et des opacités nodulaires suivies par une fibrose et une rétraction pulmonaire avec emphysème et lésions pleurales L effet fibroblastique de l aluminium sur les poumons semble moins actif et plus transitoire que celui de la silice

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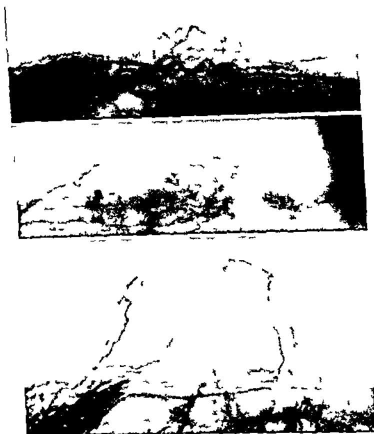


Fig 1 Illustrative examples from a growth study of transplanted squamous cell carcinoma Scarcity of vessel The resistant pattern is apparent

made manually with gentle pressure Eastman Kodak Industrial Type M film and a 0 3 mm roentgen tube were used The angiogram of the tumor and surrounding structures were enlarged ten times (linear magnification) and the photographs studied by three independent observers Tumors of the same histologic type were first examined together and various groups then compared for similarities and differences in vascular appearances

Squamous cell carcinoma

Swiss 51 mice (obtained from Dr Suntzeff of the Cancer Research division) were studied 10 with Thorotrast and 5 with Micropaque injections The choice of the contrast media did not influence the angiographic appearances

appearances from the viewpoint of the history of the tumors may add to the understanding of the behaviour of the latter The practical advantages of an indication of the histology of tumors *prior to operation are self evident* This preliminary report is based on a series of experiments in which angiography was performed in a large number of mice with transplanted and spontaneously malignant tumors The vascular systems were injected in an identical manner and the angiograms were enlarged and studied for similarities and differences The experiments were designed to determine whether (1) Specific reproducible vascular configurations exist for different neoplasms, (2) the angiographic appearances depend on the host, (3) a given tumor has a similar vascularity in different strains of mice, (4) if different types of neoplasms produce characteristic but different appearances in the same strain of mice, (5) if the vascularity remains the same while the tumor grows, and finally, (6) if spontaneous tumors have the same vascular appearances as their transplants

Material The investigation was based on the angiograms of 171 tumor bearing adult mice Angiograms of 40 additional mice were excluded either because the tumors were too small, or because the angiographies were technical failures Normal mouse angiograms, performed to develop the technique of examination, were also excluded The types of tumors examined and the strains of mice in which they grew are summarized below

Type of tumor	Host	Number of studies
Transplanted squamous cell carcinoma	Swiss 51	13
Spontaneous carcinoma of breast	C3H and Swiss 51	14
Transplanted carcinoma of breast	C3H and Swiss 51	46
Hepatoma	C57 L	24
Lymphosarcoma	C3H	29
Sarcoma — 37	DBA/1	17
Rhabdomyosarcoma	C3H	28
		Total 171

Method The tumors were transplanted into the subcutaneous tissues of the flanks of adult mice, in a few cases the transplant was made into the muscles of the thigh Micropaque (Colloidal barium sulphate) was used because it is frequently arrested in the arterioles and usually does not pass through the capillaries, it was hoped that this would afford a means of studying only the the arterial phase of tumor vascularity

The angiograms were performed with a PE 160 polythene catheter placed in the exposed left ventricle after the mice were anesthetized In the majority of cases films were obtained after the injection of 1, 2, and 4 ml Thorotrast (Testogen & Co) In thirty four mice a fine suspension of Micropaque (Daman cy & Co Ltd) was injected and a single exposure made The injections were



Fig 3 Transplanted breast tumors in mice (a) injected with Thorotrast and (b) with Micropaque The vessels have a tendency to encircle lobules Parallel small vessels ("brushes") are seen (arrows)

Thorotrast and all of the tumors injected with Micropaque had small saccular structures filled with contrast medium In 16 of the 24 hepatomas these sacs were arranged in clusters (Fig 2)

Transplanted adenocarcinomas of the breast

Thirty three adenocarcinomas of the breast in C3H mice (approximately evenly distributed between C3HBA and H2712J from Jackson Memorial Laboratory) and 4 transplanted breast tumors in Swiss 51 mice (from our Cancer Research Division) were injected with Thorotrast

Of the 9 transplanted breast tumors injected with Micropaque 8 were in C3H mice and 1 was in a Swiss 51 mouse No significant difference was apparent between the appearances of the vessels in tumors injected with Thorotrast and Micropaque or in the two strains of mice studied Grossly there was a tendency for the tumor to be lobulated The vessels on the surface of the tumor were generally not very large The tumors were somewhat less vascular than hepatomas but more vascular than squamous cell carcinomas The vessels tended to form lobules (Fig 3) In 35 of the 46 tumors (76 %) small vessels of



Fig 2 Two examples of transplanted hepatomas The vessels show a *tendency to encircle lobules Prominent saccular formations filled with* contrast medium (arrows)

which were similar in all the tumors There was a tendency for the neoplasm *to assume a rounded shape and, when large, to become cystic Large vessels* encircled the tumors to form a coarse network, the tumors themselves being poorly vascularized The blood vessels immediately below the tumour tended *to run parallel to the body surface (Fig 1) With the injections of Micropaque,* arteries and veins in the tumors were demonstrated, which suggested the presence of vessels larger than capillaries, and appeared to act as arteriovenous communications

Hepatomas

C 57 L mice with tumors (obtained from the Jackson Memorial Laboratory) were studied 19 with Thorotrast and 5 with Micropaque The Micropaque injections on the arterial side of the circulation filled veins and did not differ *from the angiograms obtained with Thorotrast Large superficial vessels were* present Grossly the tumors had a spherical shape and were raised from the body surface In 14 of the 19 mice injected with Thorotrast and in 3 of the 5 *injected with Micropaque, the vessels showed a tendency to encircle portions* of the tumor and form lobules (Fig 2) Thirteen of the 19 tumors injected with



Fig 3 Transplanted breast tumors in mice (a) injected with Thorotrast and (b) with Micropaque The vessels have a tendency to encircle lobules Parallel small vessels ("brushes") are seen (arrow)

Thorotrast and all of the tumors injected with Micropaque had small saccular structures filled with contrast medium In 16 of the 24 hepatomas these sacs were arranged in clusters (Fig 2)

Transplanted adenocarcinomas of the breast

Thirty three adenocarcinomas of the breast in C3H mice (approximately evenly distributed between C3HBA and H2712J from Jackson Memorial Laboratory) and 4 transplanted breast tumors in Swiss 51 mice (from our Cancer Research Division) were injected with Thorotrast

Of the 9 transplanted breast tumors injected with Micropaque 8 were in C3H mice and 1 was in a Swiss 51 mouse No significant difference was apparent between the appearances of the vessels in tumors injected with Thorotrast and Micropaque or in the two strains of mice studied Grossly there was a tendency for the tumor to be lobulated The vessels on the surface of the tumor were generally not very large The tumors were somewhat less vascular than hepatomas but more vascular than squamous cell carcinomas The vessels tended to form lobules (Fig 3) In 35 of the 46 tumors (76 %) small vessels of



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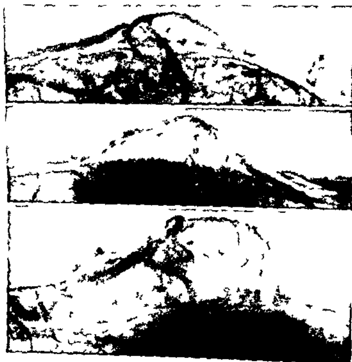


Fig 5 Three samples of growth study of *transplanted* breast tumors The char cterist cs of the vascul r ty appea *early* and do not seem to change with grow th the s milar ty with the vessels in figs 3 and 4 is striking

C3H mice failed to show the same *vascularity* evident in the transplanted breast tumors The Micropaque injected *breast* carcinoma in the Swiss 51 mouse resembled the other 12 All *tumors* showed similar brushes lobulation and vascularity The vessels *entered the* neoplasm perpendicularly and did not exhibit the parallel arrangement *beneath the* tumor evident in the transplanted breast tumors (Fig 4) The *demarcation* between the normal subcutaneous tissue and the tumor was not *sharp and* suggested infiltration

Lymphosarcoma

Twenty five C3H mice were studied with Thorotrast and 4 with Micropaque (from our Cancer Research *Division*) The tumors grew rapidly, spread parallel to the surface of the body, and were *not sharply* demarcated from the normal subcutaneous tissue The tumor vessels injected with Thorotrast were generally smaller than in the other *neoplasms studied* and tended to run parallel with the body surface (Fig 6) Fine *vascular* structures aro e perpendicularly from

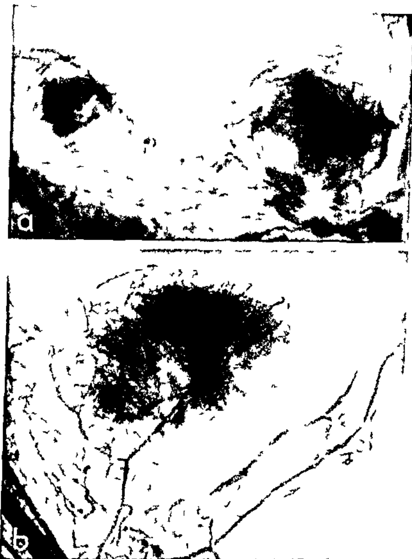


Fig 4 Two examples of spontaneous breast tumors (a) in a C3H mouse injected with Thorotrast and (b) in a Swiss 51 mouse injected with Micropaque Both tumors are similar in appearance with same vascular characteristics as in transplanted breast tumors (Cf fig 3) Brushes are again seen

variable caliber densely arranged in a parallel fashion with 'brush like' structures were noted They surrounded the tumor lobules and formed multiple *tufted areas throughout the tumor*

Spontaneous adenocarcinomas of the breast

Thirteen spontaneous adenocarcinomas of the breast in C3H mice were examined with Thorotrast and 1 spontaneous breast tumor in a Swiss 51 and 1 in a C3H mouse with Micropaque Only 2 of the 14 spontaneous tumors in





Fig 7 Two examples of sarcoma 37 Irregular arrangement of vessel numerous lakes (arrows) In (a) vascular candelabra arrangement (↔)

channels lying parallel to the body surface We called this arrangement candelabra (Fig 7)

Rhabdomyosarcoma

Twenty tumors in C3H *mice* were studied with Thorotrast and 8 with Micropaque (from our Cancer Research Division) The tumors were not sharply demarcated and the supplying vessels entered them perpendicularly When studied with Thorotrast the vessels in the tumors were numerous and

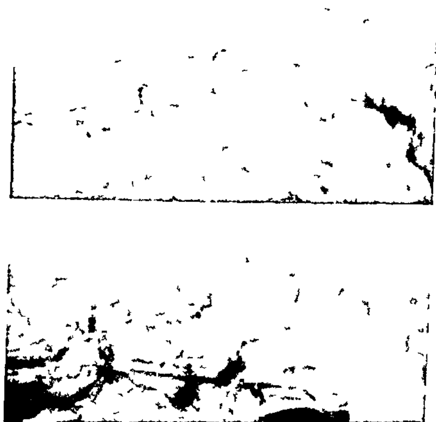


Fig 6 Two representative Thorotrast injections of lymphosarcoma Parallel arrangement of vessels forming layers

these vessels and ran toward the surface The large veins draining the tumors were somewhat tortuous but had the same parallel orientation to the surface of the body In the tumors injected with Micropaque only the arteries were visible and these also ran in a parallel direction to the body surface, no fine vascular structures were identified Conclusions regarding the presence or absence of channels larger than capillaries cannot be drawn from this small series

Sarcoma 37

Fourteen tumors in DBA 1 mice (from Jackson Memorial Laboratory) were studied with Thorotrast and 3 with Micropaque The contrast medium used did not alter the angiographic appearances The vessels below the tumor ran parallel to the surface of the body and those in the tumor were numerous, markedly irregularly distributed, and large There were numerous ill defined areas ('lakes') filled with contrast medium throughout the neoplasms Some of the tumors had vessels running perpendicularly into large superficial vascular

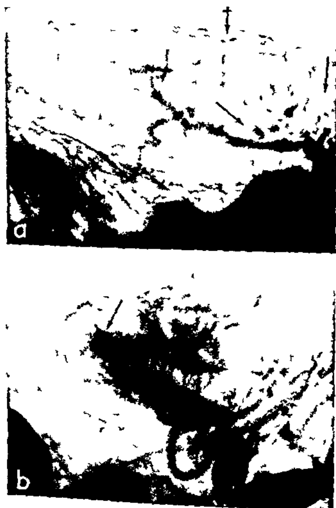


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Fig 8 Examples of transplanted rhabdomyosarcomas The irregular arrangement of vessels is similar to that seen with sarcomas (cf fig 7) Numerous lakes (arrows) a) Subcutaneous inoculation and b) intra muscular inoculation in thigh tibia (↦) and femur (arrow marked with star in the middle of the tumor) did not differ in vascular arrangement

irregular 'Lakes' were present in 17 of the 20 tumors studied The arrangement of the vessels was markedly irregular The vessels were generally larger but similar to those seen in sarcoma 37, the differentiation is usually not possible by angiography (Fig 8)

Studies with Micropaque in which the injection was entirely on the systemic arterial side presented a completely different angiographic pattern Only arteries were seen in the tumor and no filled veins nor 'lakes' were present Although the general arrangement of the vessels was still irregular, the angio graphic appearances differed significantly from those obtained by injection

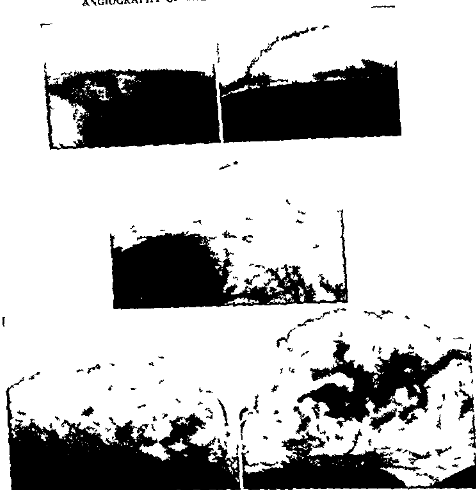


Fig 9 Illustrative angiograms from a growth study of rhabdomyosarcomas (Cf fig 8)

with Thorotrast No definite conclusions can be drawn from such scanty material but the problem of arteriovenous communications in rhabdomyosarcomas needs further investigation by microangiography

Growth studies

Angiography was also performed in tumor bearing mice at various stages of tumor growth It was desired to establish the angiographic changes that occur with growth and determine the time when a characteristic angiographic pattern is evident Three transplantable tumors were selected for this purpose rhabdomyosarcoma adenocarcinoma of the breast and squamous cell car

cinoma of the skin Equal transplants of the tumor were inoculated into large groups of mice and angiography was performed by the method described Rhabdomyosarcoma bearing mice were studied at two day intervals starting on the third day after the transplantation of the tumor and were carried through the twenty sixth day Breast tumor growth studies were started on the seventh day following transplantation The examinations were performed every third day and were carried through the twenty eighth day The group of Swiss 51 mice that was inoculated with squamous cell carcinomas was studied at four day intervals in the beginning of the study and later at two day intervals The time of study was between the seventh day and the twentieth day after transplantation

The basic features of the vascular arrangements appeared early and were unchanged during growth (Figs 1, 5 and 9) As squamous cell carcinomas became cystic they showed fewer vessels Similar studies are being conducted on other tumors

Conclusions

Tumors of mice studied by angiography appeared to have characteristic vascular arrangements, these being similar in those having common histologic features, such as sarcomas 37 and rhabdomyosarcomas or, to a lesser extent, hepatomas and breast carcinomas Spontaneous breast carcinomas presented the same angiographic appearances as transplanted mammary gland carcinomas Spontaneous and transplanted carcinomas of the breast, lymphosarcomas and rhabdomyosarcomas had specific and characteristic angiographic appearances in spite of the fact that they all grew in the same strain of mice (C3H) There was no definite difference in the vascularity of carcinomas of the breast whether they were present in C3H or Swiss 51 mice Growth studies of rhabdomyosarcomas, carcinomas of the breast, and squamous cell carcinomas indicated that their vascular arrangement started early in the course of their growth and did not change Rhabdomyosarcomas presented the same vascular appearances whether transplanted subcutaneously or intramuscularly More work is needed to study arteriovenous communications in the tumors in order to correlate the minute histologic and angiographic appearances, and to clarify the nature of the 'lakes', 'brushes', and lobulation Microangiographic investigations of tumors in mice are being conducted

Acknowledgement

We wish to express our thanks to Dr Valentina Suntzeff for her invaluable help and suggestions and for supplying some of the tumor bearing mice to Dr Michel Ter Pogossian for his guidance in solving many of the technical problems and to Mr Cramer Lewis who provided the photographic enlargements and reproductions The investigation was supported by a grant from the American Cancer Society

SUMMARY

A preliminary report of angiographic studies on 171 adult tumor bearing mice is presented Characteristic angiographic appearances of various tumors were established and are described The vascularity of transplanted adenocarcinomas of the breast rhabdomyosarcomas and squamous cell carcinomas were examined at specified intervals during their growth

ZUSAMMENFASSUNG

Ein vorlaufiger Bericht uber angiographische Studien an 171 ausgewachsenen tumorkranken Mausen wird vorgelegt Charakteristische angiographische Befunde verschiedener Tumoren wurden festgelegt und werden beschrieben Der Gefassreichtum transplantierter Adenokarzinome der Brust von Rhabdomyosarkomen und Plattenepithelkarzinomen wurde mit bestimmten Intervallen wahrend ihres Wachstums untersucht

RÉSUMÉ

Les auteurs présentent une note préliminaire sur l étude angiographique de 171 souris adultes porteuses de tumeurs Ils ont établi et décrivent les aspects angiographiques caractéristiques de diverses tumeurs Ils ont examiné la vascularisation d adénocarcinomes du sein de rhabdomyosarcomes et d epithéliomas malpighiens différenciés transplantés a des intervalles déterminés au cours de leur croissance

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16 WICKBOM I Angiographic demonstration of tumor pathology Acta radiol 40 (1953) 529

FROM THE ROENTGEN DEPARTMENT (DIRECTOR DOCENT P VIRTAMA) OF MEDICAL CLINIC II (DIRECTOR PROF I VARTIAINEN), UNIVERSITY CENTRAL HOSPITAL, HELSINKI FINLAND

INFLUENCE OF CERTAIN PHYSICAL FACTORS ON THE RADIOGRAPHIC DEMONSTRATION OF CHOLESTEROL GALLSTONES

by

PEKKA VIRTAMA

Roentgen examination of the gallbladder is a reliable method and one in which the roentgenologic and operation findings are in agreement in more than 90 per cent of cases The roentgen technique is well established but the exact role played by certain physical factors in demonstration of small gall stones particularly the concentration of iodine in the gallbladder and the tube voltage used is not quite clear HORNYKIEWYTSCH and STENDER (1953) recommended an exposure of 120 to 200 mAs at 60 to 65 kV in intravenous cholegraphy while COCCHI (1953) and WEGELIUS et coll (1954) advocated the use of a high voltage technique in cholecystography SAMUEL (1960) expressed the fear that the high density produced by certain new cholegraphic contrast media might not be entirely advantageous because small stones might be obscured The introduction of these new compounds would therefore appear to justify a re appraisal of the radiographic technique with special regard to the importance of the tube voltage in the demonstration of small gallstones

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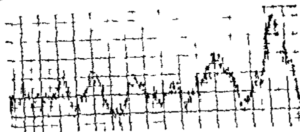


Fig 3 Densitometric curve recorded from image in fig 6d Concentration of Biligrafin 5 0 g/100 ml kV 50 mAs 2 000

(Tensol cement ICI) and the plate with the stones (Fig 1) was dipped into the contrast medium in the perspex tube which was placed in the water in the large perspex tray (Fig 2)

The contrast media examined were Biligrafin (Schering), Solu Biloptin (Schering) and Bilijodon Natrium (Leo) which were diluted with water to the following concentrations 0 2 0 5 1 0 2 0 5 0 and 7 0 g/100 ml

A three phase roentgen apparatus the Siemens Tridoros was used The roentgen tube was fitted with two foci the effective size of which were 0 3 and 1 0 mm² as given by the manufacturers FFD 75 and 150 cm field sizes 9 × 12 and 18 × 24 cm A stationary cross grid was used The voltages were 50 60 70 80 90 and 100 kV The mAs values were adjusted so as to give a background density of 1 2 density units, as produced by a 18 cm thick water layer The highest mAs value used was 2 200 at 50 kV Kodak's Blue Brand roentgen film and Siemens Rubin fine grain intensifying screens were employed throughout the study the films were developed in DX 80 developer at 20 C with intermittent manual agitation for 4 min Fixing washing and drying were carried out in the usual way

To obviate any subjective bias in judging the visibility of the stones the films were analysed with the aid of a doublebeam recording densitometer (Joyce & Loebl & Co Ltd Newcastle upon Tyne England) A scanning line crossing the roentgen images of the stones was recorded from the films The ratio of the lever connecting the densitometric table with the recording pen was 1 to 2 so as to give a × 2 enlargement Each stone caused a certain deflection in the densitometric curve (Fig 3) The height and the width of the deflection caused by a just detectable stone was determined with the aid of several blind tests by five independent observers It was thus possible to register the smallest stone detectable from the densitometric curves

Results

The diameters of the smallest stones detectable in various conditions are seen from Table 1 The arithmetic means of the values obtained with different concentrations of the contrast media and at the voltages used were calculated

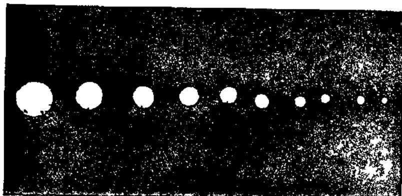


Fig 1 Artificial cholesterol stones used in the experiments

Material and Methods The equipment used was experimental A large perspex tray, 18 × 34 × 35 cm in size and filled with water, was used as a soft tissue phantom, the absorbing mass of the phantom was in effect considerably larger than that of a medium sized patient A long square perspex tube, measuring 2 5 × 2 5 × 25 0 cm, acted as a gallbladder and was filled with various concentrations of cholegraphic contrast media

The smallest gallstones are usually *non calcified cholesterol or cholesterol* pigment stones (EPPRECHT et coll 1953, and others) Suitable artificial stones were made from 75 % cholesterol and 25 % gelatine mixed at 65 to 70° C, formed into rounded pellets of various sizes, and surface hardened by being steeped in 10 % formalin for 12 hours The absorption qualities of the artificial stones were compared with those of pure cholesterol by examining them at the voltages used in the course of this study with equal amounts of cholesterol No difference was evident

The diameters of the stones examined were 1 0, 2 0, 2 5, 3 0, 4 0, 4 5, 5 0, 6 0, 7 0 and 10 0 mm They were fixed on a perspex plate with perspex cement

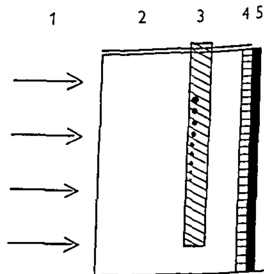


Fig 2 Experimental arrangement 1 — Roentgen rays 2 — Perspex tray filled with water 3 — Perspex tube containing contrast medium and cholesterol stones 4 — Cross grid 5 — Cassette with film

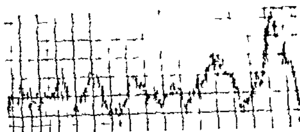


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Results

The diameters of the smallest stones detectable in various conditions are seen from Table 1 The arithmetic means of the values obtained with different concentrations of the contrast media and at the voltages used were calculated

Table 1

Effect of kV and concentration of various contrast media on the demonstration of gallstones

Concentration	kV	Diameters (mm) of smallest stones discernible with different media: Biligrafin	Solu Biloptin	Biliodon Natrium	Mean
0.2 g/100 ml	50	3.0	3.0	3.0	3.0
	60	3.0	3.0	3.0	3.0
	70	3.0	3.0	3.0	3.0
	80	4.0	4.5	4.5	4.3
	90	4.5	4.0	4.5	4.6
	100	5.0	4.5	5.0	4.8
0.5 g/100 ml	50	2.5	2.0	2.0	2.3
	60	2.5	2.5	2.5	2.5
	70	3.0	3.0	3.0	3.0
	80	3.0	3.0	4.0	3.3
	90	3.0	4.0	4.0	3.6
	100	4.5	4.5	4.5	4.5
1.0 g/100 ml	50	2.0	2.5	2.5	2.3
	60	2.5	2.5	2.5	2.5
	70	2.5	2.5	2.5	2.5
	80	3.0	3.0	4.0	3.3
	90	4.0	4.0	4.0	4.0
	100	4.5	4.5	4.0	4.3
2.0 g/100 ml	50	2.0	2.0	2.0	2.0
	60	2.0	2.0	2.0	2.0
	70	3.0	3.0	2.5	2.8
	80	3.0	3.0	3.0	3.0
	90	4.0	3.0	3.0	3.3
	100	4.0	4.5	4.5	4.3
5.0 g/100 ml	50	1.0	1.0	1.0	1.0
	60	1.0	1.0	1.0	1.0
	70	2.0	2.0	2.0	2.0
	80	2.5	2.5	2.5	2.5
	90	3.0	3.0	2.5	2.8
	100	4.0	4.0	4.0	4.0
7.0 g/100 ml	50	1.0	1.0	1.0	1.0
	60	1.0	1.0	1.0	1.0
	70	2.0	1.0	2.0	1.6
	80	2.5	2.0	2.0	2.2
	90	3.0	3.0	3.0	3.0
	100	3.0	4.0	3.0	3.3

The mean diameters of the smallest stones detectable were plotted against the tube tension (Fig. 4) and the concentration (Fig. 5). The smallest stone, 1 mm in diameter, was discernible at 50 and 60 kV in concentrations of 5.0 g/100 ml or more. The size of the smallest stone demonstrable at 50 to 60 kV was about half the size of the stone visible at 100 kV in the same concentration. The effect of the concentration of the contrast medium was especially marked

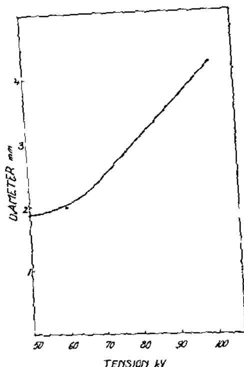


Fig 4 Arithmetic means of diameters of smallest stones detectable at various tube tensions

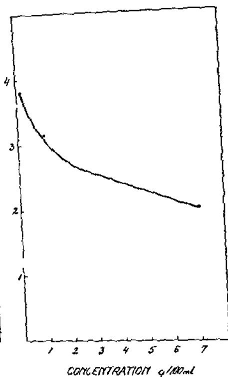


Fig 5 Arithmetic means of diameters of smallest stones detectable in various concentrations of contrast media

in low concentrations and the detectability of the stones was considerably impaired in concentrations less than 1 0 g/100 ml

The results were analysed according to standard statistical methods A highly significant correlation between the size of the smallest stone detectable and the concentration of the contrast medium and the voltage used was found at the level of $P < 0.001$ This means that the detectability of the stones was impaired by low concentration of the contrast medium and by high voltage (Figs 4 5 and 6) There were no significant differences in this respect between the contrast media examined

Effects of the focal size of the roentgen tube the FFD and the field size were analysed in the same manner The results obtained by the statistical analysis are given in Table 2

Discussion

All gallstones cannot be demonstrated roentgenologically There is a limit size in cholesterol concretions detectable which is dependent on the radiographic technique used It is obvious from the results obtained that factors

Table 2

Effect of field size, focal size and FFD on demonstration of gallstones

		Mean diameter (mm) of stone visible		Mean diameter (mm) of stone visible	P
Field size	18 × 24 cm	3.7	9 × 12 cm	3.1	0.0[illegible]
Focal size	1 × 1 mm	4.1	0.3 mm²	3.3	0.01
FFD	150 cm	3.3	75 cm	3.7	

increasing radiographic definition and contrast improve the detectability of small cholesterol stones. The following conclusions may be drawn.

A fine focal spot, 0.3 mm in diameter, significantly improves the detectability of cholesterol concretions by decreasing the geometrical blurr as compared with 1 mm of focal spot in diameter.

A small field size (9 × 12 cm) increases the radiographic contrast (MORGAN 1946) thus also increasing the detectability of gallstones.

Low voltage and high concentration of iodine in the gallbladder improve the results significantly by increasing the radiographic contrast.

A high voltage technique is advantageous in the roentgen examination of the gastrointestinal tract with barium sulphate owing to the increased penetrability of the roentgen rays, as shown by GIANTURNO (1950) and BUCHER (1952). However, this does not wholly apply to examinations with iodine

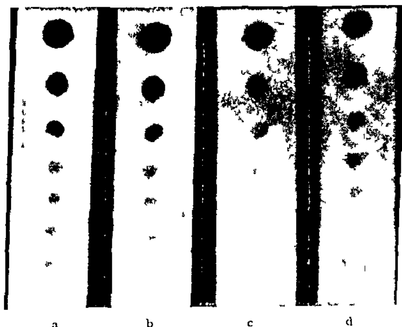


Fig. 6. Roentgen images of phantom gallbladder. a), b) and c) at a concentration of 5.0 g/100 ml Biligrafin and with tube tensions of 50 kV, 70 kV and 100 kV respectively. d) at a concentration of 0.2 g/100 ml Biligrafin and tube tension 50 kV.

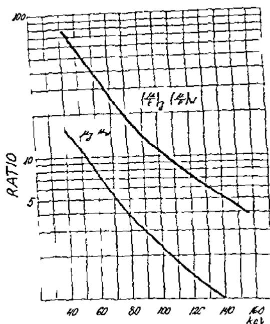


Fig 7 Ratio between linear absorption coefficients (μ) and mass absorption coefficients ($\frac{\mu}{\rho}$) of iodine and water at different monochromatic radiation energies

containing compounds because of their absorption characteristics As seen from Fig 7 the linear absorption coefficient of iodine (MORGAN & CORRIGAN 1955) is very near to that of water at about 150 kV

Only about 5 per cent of the orally administered diiodo contrast medium is excreted in the bile this becoming 36 per cent with intravenously administered Biligrafin (BILLION 1954) The concentration of the former in the gallbladder does not therefore exceed 0 3 g/100 ml while the concentration of the latter may be as high as 6 to 7 g/100 ml (FROMMHOLD 1953) It is apparent that voltages higher than 70 to 80 kV cannot be recommended in oral cholegraphy while in intravenous examinations voltages up to 100 kV give approximately the same result owing to the high concentration of iodine in the gallbladder as seen from Table 1 Furthermore in uncertain cases when gallstones are probable but are not confirmed an intravenous examination rather than a further oral examination is advisable This is particularly valid when the size of the subject requires a large exposure because the higher concentration of the contrast medium renders it possible to use a relatively high kilovoltage Very high mAs values are not feasible in practice by reason of the increased blurring and loading of the roentgen tube caused by long exposure times

Small cholesterol concretions may obviously be obscured by underexposure of a dense gallbladder However, with the aid of the increased density produced by the new triiodo compounds, the results of cholegraphy may further be improved, provided that the radiographic technique is adjusted so as to give maximum contrast and definition

Acknowledgements

The author wishes to express his thanks to Prof O Eränkö for permission to use the densitometer of the Department of Anatomy to Dr Gisela Gastrin for valuable technical assistance to A Muroma M A for the statistical analysis and to Oy Medica AB Helsinki who manufactured the artificial stones

SUMMARY

The visibility of artificial cholesterol stones was investigated with the aid of phantom experiments The diameter of the smallest stone discernible was 1 mm The best results were obtained at relatively low voltages and high concentrations of contrast media Factors increasing the radiographic contrast and definition improved the possibilities of demonstrating the stones

ZUSAMMENFASSUNG

Die Sichtbarkeit kunstlicher Cholesterinsteine wurde mit Hilfe eines Phantomexperiments untersucht Der Durchmesser der kleinsten erkennbaren Steine war 1 mm Die besten Resultate wurden bei relativ niedrigen Spannungen und bei hohen Konzentrationen des Kontrastmittels erzielt Faktoren welche den rontgenographischen Kontrast und die Auflosung steigern verbesserten die Moglichkeiten die Steine zu demonstrieren

RÉSUMÉ

La visibilité de calculs de cholestérol artificiels a été étudiée par des essais avec un fantôme Le plus petit calcul visible avait un diametre d un millimètre Les meilleurs résultats ont été obtenus avec des tensions relativement basses et une forte concentration de moyen de contraste Les facteurs qui augmentent le contraste radiographique et la définition ont amélioré les possibilités de mettre les calculs en évidence

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FROM THE FORMER CHIEF (W. HONDIUS BOLDINGH) OF THE X-RAY DEVELOPMENT LABORATORY OF N. V. PHILIPS' GLOEILAMPEN FABRIEKEN, EINDHOVEN, HOLLAND

QUALITY AND CHOICE OF POTTER BUCKY GRIDS
PART VI

by

W. HONDIUS BOLDINGH

VI. Exposure data for various grids

For the preceding articles in this series the reader is referred to Parts I—III (BONENKAMP & HONDIUS BOLDINGH 1959) and Parts IV—V (HONDIUS BOLDINGH 1961).

Ever since the advent of medical radiography exposure tables for the various parts of the body have been employed. These tables originally comprised data suitable for a particular installation, and not until reliable control of the voltage had been achieved did the tables become more universally applicable. Reproducible and comparable voltages were obtainable after World War II, but even then only in those cases in which adequate allowance for any mains voltage drop had been made.

Although most exposure tables indicate when a grid should be employed, they generally contain no detailed specification for the grid itself; in some charts a factor for grids of given ratios may be indicated by which the basic mAs values (without grid) should be multiplied. Information of this kind would be of value only if it were a fact that the factors were the same for all grids of the same ratio, irrespective of object and exposure conditions. But such is not the case. For a grid of a given ratio, the Bucky factor depends to a large extent on the strip density (number of strips per cm), the thickness of the object, the width of the beam, and the voltage. This is clearly shown in Table I, in which

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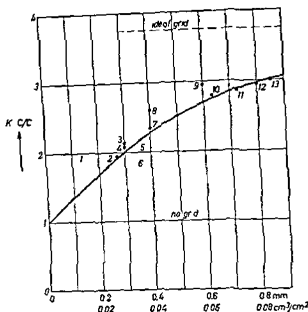


Diagram 1 Contrast improvement factor K (100 kV d = 20 cm H O) as a function of the lead content
(This graph appears also in Vol 55 p 32 of Acta Radiologica)

the Bucky factors B are given for light and heavy grids at 60, 100 and 200 kV the factors have been determined with a wide beam in water phantom thicknesses of 10 20 and 30 cm

Table

Bucky factors of various grids for different tube voltages and different phantom thicknesses

	10 cm H O	20 cm H O	30 cm H O
60 kV	2 3–3 5	2 5—6 0	3 7—7 2
100 kV	2 1—3 2	2 5—5 0	3 0—6 6
200 kV	1 9—2 9	2 1—4 3	2 6—5 1

Other charts may prescribe voltage increase for grids of given ratios but such recommendations are unsuitable for nearly the same reasons as given above It is also a fact that no general value can be attached to the recommendation to employ coarse or fine grids, since there are grids that require the same exposure times whether they contain relatively few (25) or many (40) strips per cm

It is perhaps surprising that the various recommendations for the use of grids have not introduced more difficulties in actual practice but this may be

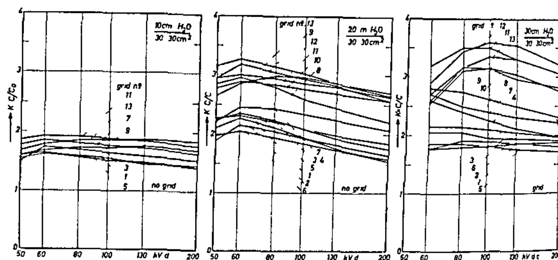


Diagram 2 Contrast improvement factor as a function of the tension
(These graphs appear as diagram 3 in Vol 55 p 231 of Acta Radiologica)

due to the fact that, as long as the various types of grids were of the same low ratio, the exposure data did not differ much A great variety of grids of different types and designs have, however, recently become available, and many roentgen couches and stands are designed for use with interchangeable grids, so that the radiologist may to day be forced into the same situation as in earlier days as soon as he brings a new type of grid into use he may have to compile a new exposure table An indication of the ratio of a grid will not be sufficient, even less so than in earlier days, for an adequate determination of the required exposure data

The *contrast improvement factor*, introduced in Part V (HONDIUS BOLDINGH 1961) can help us out of this difficulty It may be recalled that this factor, K, is determined by the quotient when the contrast obtained with grid is divided by the contrast without grid

$$K = C/C_0 ,$$

determined under standard conditions This factor is of value not only because it constitutes a direct measure of the contrast improving capacity of the grid, but also because it may be correlated in a simple way to the exposure data

As may be seen from Diagrams 1 and 2 (reproduced from Diagrams 3 and 4 in Part V, pp 231 and 232), the contrast improvement factors for six of the thirteen grids, measured at 100 kV in a 20 cm water phantom (K_{100}) differ only slightly, their values being 1 85, 1 95, 1 95, 2 10, 2 10, and 2 10, respectively As was also mentioned in Part V, differences of a few tenths in K_{100} are barely perceptible and thus of little significance in medical practice These six grids belong to the group of light grids, with lead contents between 0 015 and 0 038 cm³/cm², i e 0 15 to 0 4 mm in round figures However this is not the only

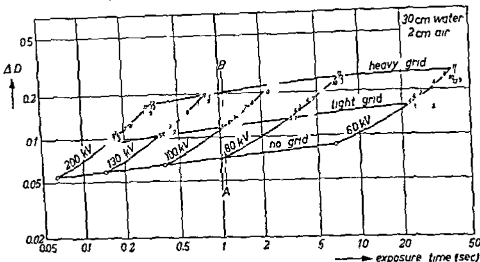


Diagram 3 Contrast ΔD as a function of exposure time from 60 to 200 kV Bottom line no grid second line lightest grid top line heaviest grid Numbers 1 to 13 correspond to the grids used in the measurements numbered in sequence of their lead content
(This graph appears also in Vol 57 p 151 of Acta Radiologica)

property that these grids have in common As may be seen from Diagram 3 (reproduced from Diagram 1 in Part II p 151) the exposure times at the same voltage tube load and film blackening, even with a 30 cm water phantom do not differ much from a mean value The fact that the results with all these grids are in conformity could offer an explanation why only vague indications for the use of grids are given in most exposure tables as they may have been derived from measurements with grids perhaps varying in type but all belonging to the group of 'light grids

As appears from Table I and Diagram 3 heavier grids may require exposure times twice as long as those required for lighter grids at the same voltage This is not a constant factor, however and such a big increase in the exposure time is moreover often unacceptable It was stated previously (Part I p 188) that the requisite increase in exposure time may be compensated for by a voltage increase and then only a small part of the contrast improvement need be sacrificed Now it is a fortunate fact based on empirical observations that these voltage increases depend to a considerably smaller degree than the Bucky factor on the object thickness and that within reasonable limits they are simply and linearly related to the contrast improvement factor K_{100} particularly so if cross grids be excluded from the comparison

The measurements with eleven linear grids using 10 20 and 30 cm water phantoms are given in Diagram 4, the required voltage for exposures with

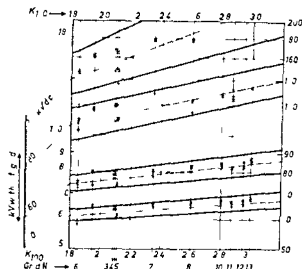


Diagram 4. Voltage as a function of the contrast improvement factor K_{100} for equal exposure times, tube load and film blackening for eleven linear grids (vertical lines) at different thicknesses of a 30 × 30 cm² water phantom.

Denotations × 10 cm water phantom
20 cm » »
— 30 cm » »
— — — Average for all object thicknesses
——— Tolerance lines corresponding to 25 shorter and longer exposure times than the average values.

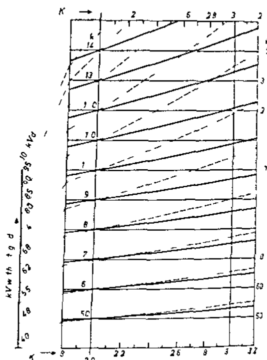


Diagram 5. Voltage (kV) as a function of the contrast improvement factor of linear grid for given exposure times and film blackening. The averages for all object thicknesses are indicated by — — — for equal tube load (kW) and ——— for equal tube current (mA and mAs).

grid being given as a function of K_{100} and compared with the values obtained at 50, 60, 80, and 100 kV without grid (on the extreme left). The graph in Diagram 4 has been constructed on the basis of the measurements described in the earlier parts, in which the Bucky factors and the relationship between mAs and kV were obtained with equal tube load and the same film blackening.

As regards the deviations from the straight line average of the individual values (denoted by the symbols ×, , and —) for the three different thicknesses (broken lines in Diagram 4) it should be remembered that voltage differences corresponding to a reduction or increase by about 25 % of the mAs values cause no appreciable difference in film blackening. This tolerance is *indicated by the fully drawn lines in Diagram 4.*

The (approximate) independence of the voltage increase with respect to object thickness may be explained as follows. Although the Bucky factor requiring compensation might be greater with thicker objects, the requisite voltage increase will be less because of the fact that when radiation passes through a thicker object it becomes harder, due to filtration.

When therefore the value of K_{100} of a heavy grid is known, it becomes possible with the aid of a simple rectilinear graph (Diagram 4) and an exposure table compiled for light grids to determine the voltage to be applied with a heavy grid in order to attain equal film blackening with the same exposure times and tube loads as given for the light grids Diagram 5 is even more suitable for this purpose since lines are drawn from 50 to 140 kV for light grids (K_{100} = 2 0) For the sake of completeness the corresponding voltages for exposures without grid are also indicated on the extreme left of this diagram

The broken lines in Diagrams 4 and 5 apply to constant tube loads (isowatt), and are therefore suitable for operating the roentgen tube under full load At the higher voltages required for exposures with a heavier grid the tube current has to be reduced proportionally with the exposure time kept constant It is evident on the other hand that if the voltage increase required for a heavier grid can be applied with the same tube current and yet without endangering the tube through overloading a smaller voltage increase will suffice In such a case the fully drawn lines in Diagram 5 apply while the interrupted lines are again applicable with constant tube load

The graphs in Diagrams 4 and 5 are based on measurements with d c voltages When pulsating voltages are used the voltage increase required for exposures with grid will differ but the differences in voltage increments between light grids with K_{100} = 2 0 and heavier grids e g with K_{100} = 3 0 are not so large as to require a different graph

If the contrast improving capacity were inscribed on all grids by the value of K_{100} this would enable uniformity to be attained between exposure tables as far as the use of grids is concerned Exposure data for grids could then always be based on those of light grids with $K_{100} = 2\,0 \pm 0\,2$ For heavier grids Diagram 5 could then be applied and the requisite voltage increases obtained by drawing vertical lines corresponding to the K_{100} value for the grids in question

Let us take for example the heaviest grid in our measuring series (13) which has the following specification

$$\underline{n = 27/cm} \quad R = 15 \quad \underline{f_1 - f_0 - f_2 = 80-90-100 \text{ cm}}$$

$$P = 0\,085 \text{ cm}^3/\text{cm}^2 = 0\,85 \text{ mm} \quad \underline{K_{100} = 3\,0}$$

Here the underlined values indicate all the properties that must be known for day to-day work the other values being only of secondary importance

The vertical line (K_{100} = 3 0, to the right in Diagram 5) applies to this grid and indicates the recommended alternative tube voltages instead of a light grid (K_{100} = 2 0) at 50 60 80 100 120 kV one should choose
54 65 90 119 152 kV for constant tube load
53 64 86 109 133 kV for constant tube current

SUMMARY

It is suggested that indications for the use of grids should be referable to light grids with $K_{100} = 2\ 0 \pm 0\ 2$ (determined under standard conditions) For obtaining roentgenograms of equal blackening and with equal exposure times when using heavier grids the values of the higher tube voltages required may be obtained from a simple rectilinear graph that is suitable for all object thicknesses

ZUSAMMENFASSUNG

Der Verfasser schlagt vor dass sich Angaben uber den Gebrauch von Rastern auf leichte Raster mit einem Kontrastverbesserungsfaktor $K_{100} = 2\ 0 \pm 0\ 2$ (unter genormten Bedingungen bestimmt) beziehen sollten Zur Herstellung von Rontgenbildern mit gleicher Schwarzung und mit gleichen Exponierungszeiten bei Benutzung schwererer Raster konnen die dafur erforderlichen hoheren Röhrenspannungen in einer einfachen geradlinigen graphischen Tabelle welche fur samtliche Objektdicken geeignet ist abgelesen werden

RÉSUMÉ

L auteur propose que les indications pour l emploi des grilles se rapportent aux grilles légères avec un facteur d amélioration du contraste $K_{100} = 2\ 0 \pm 0\ 2$ (déterminé dans des conditions standard) Pour obtenir une radiographie de même noircissement avec le même temps de pose quand on utilise une grille plus lourde on peut déterminer la tension plus élevée qui est nécessaire au moyen d un simple graphique rectiligne valable pour toutes les épaisseurs d objet

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FROM THE DEPARTMENT OF GYNAECOLOGY (DIRECTOR ASSOCIATE PROF H L KOTTMEIER) AND THE INSTITUTE OF RADIOPATHOLOGY (DIRECTOR. PROF L. SANTESSON) RADIUMHEMMET STOCKHOLM SWEDEN

CLINICAL ASPECTS OF DYSGERMINOMA OF THE OVARY

by

SAM BRODY

The ovarian dysgerminoma belongs to the group of germ cell tumours (38) Much confusion has prevailed concerning the histogenesis and histopathology of tumours belonging to this group and conflicting views have been expressed as to their structural interrelations The histogenetic concept of TEILUM is now accepted by many authors for their classification

The less differentiated tumours of this group i e embryonal carcinoma mesoblastoma (38) mesonephroma ovarii (30) and chorioepithelioma are highly malignant and have an almost invariably fatal course (29) A dysgerminoma on the other hand exhibits a special and considerably more uniform histologic structure From a clinical point of view as well it constitutes a special group within the germ-cell tumours as is also the case with the corresponding seminomas of the testis Although a dysgerminoma is a neoplasm displaying clearly malignant features in terms of proliferative capacity destructive growth with infiltration of the pelvic organs and a strong tendency to metastasize and recur its degree of malignancy and response to various therapeutic procedures have been the subject of widely divergent opinions (15 19 25 28) Thus the reported five year survival rate varies from 27 3 to 66 6 per cent

Submitted for publication 5 April 1961

Table 1

Age distribution and prognosis (60 cases)

Age in years	Number of patients	Five year survival rate (%)	Recurrence rate (% of living)
10—19	16	61	50
20—29	30	83	25
30—39	8	87	0
40—49	6	50	67

The reason for this considerable discrepancy in the prognosis has not previously been analysed in detail. Apparently several factors contribute to the conflicting therapeutic results. The rarity of the tumour, with mostly only a few cases investigated in the different series, has rendered difficult a proper evaluation of its clinical malignancy. Where larger series have been studied (15,19, 25, 28), the cases have usually been collected from reports in the literature. The heterogeneity of these materials as regards principles in diagnosis and treatment have necessarily affected the conclusions drawn as to prognosis.

There is one particular aspect which emphasizes the need for a proper evaluation of the degree of malignancy displayed by these tumours. The fact that dysgerminoma mostly occurs in young women, where preservation of the reproductive function is highly desirable, makes the decision as to the extensiveness of the therapeutic procedure to be undertaken a very important one. The question is whether there is justification for conservative treatment with preservation of the function of an apparently normal contralateral ovary, or whether the malignant potentialities of these tumours call for radical treatment in all cases. Conflicting opinions have been expressed as to the role of radiotherapy in the treatment. The problem of surgery alone or its combination with post operative radiotherapy will therefore be discussed. Another question which will be considered in some detail is the genetic risk involved in conservative radiotherapeutic measures undertaken to avoid direct irradiation of an apparently normal ovary left after unilateral oophorectomy.

Material. This material comprises 60 patients, the earliest treatment dating back to 1921. The last patient was admitted to the hospital in 1959. It is an extension of the series presented by SANTESSON in 1947. As Radiumhemmet is mainly an institution specializing in radiotherapy, the cases admitted for treatment had been operated upon in other hospitals. In every instance the surgical specimen was subjected to pathologic examination. The final diagnosis, except in one patient who had been operated upon abroad, has been made by Prof. Santesson. It should be mentioned that in 3 patients only small parts of the tumours were sent for microscopic investigation. Sections from these parts contained pure dysgerminomatous structures.

Table 2

Clinical findings (60 cases)

	Number of patients	Per cent
Abdominal enlargement	18	30
Diffuse abdominal pain	19	32
Loss of weight	9	15
Abdominal mass	11	18
Acute onset	9	15
Pleural effusion	3	5
No symptoms or signs	8	13

Dysgerminoma is predominantly found in young patients The age distribution in the present series is shown in Table 1 Twenty seven per cent of the patients were under 20 and 77 per cent under 30 years of age

The menarche usually occurred between 12 and 17 years of age In the majority of cases the menstruations were normal In 5 patients no bleeding had ever occurred Of these patients 2 had genital malformations and 3 were under 14 years of age In 4 patients meno metrorrhagia was observed for various periods of time before the tumour was diagnosed In 9 cases no menstrual data were available

Thirteen patients had been pregnant once twice or three times before the appearance of the tumour In 7 patients the tumour was diagnosed in connection with pregnancy In one of these patients obstruction of the birth canal was caused by the tumour and the patient had to be delivered by caesarean section In the other cases the diagnosis was made during the puerperium All except one of these patients were primiparas In an additional case a recurrence was diagnosed and operated upon 6 weeks after interruption of pregnancy

Developmental changes in the genital sphere were observed in 5 patients In one of these both ovaries and uterus were absent and in another there was an aplastic uterus Two patients had hypoplastic uteri one of these being bicornate And in one patient a septate vagina and a lightly bicornate uterus was found

Clinical picture

The tumour may be characterized by its insidious and undramatic development In a large number of patients no discomfort was noticed and the neoplasm was accidentally diagnosed at routine check up examinations In the majority of cases the only complaint was enlargement of the abdomen sometimes associated with diffuse abdominal pain and loss of weight Some patients were aware of an enlarging firm mass in the lower abdomen

In 9 instances the onset was sudden with intense constant unilateral pain mostly in the lower abdomen and radiating down the thigh These patients were sometimes in a state of shock and had fever They were in the main

Table 1

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Table 4

Localization of metastases (60 cases)

	Number of patients	Per cent
Retroperitoneal	5	8
Pelvic*	19	32
Abdominal*	13	20
Mediastinal*	3	5
Pulmonary	3	5
Hepatic	6	10
Ovarian	7	12
Skeletal	3	5
Supraclavicular	5	8
Inguinal	4	7

* Exact localization as to organ not possible

genic dissemination however occurred as well Metastases were found in the liver lungs and ovary (metastasis or bilateral primary foci) In 3 patients involvement of the skeletal system was noted A summary of the frequency of metastases in various locations is given in Table 4

Treatment

All the patients referred to us had previously been operated upon in outside hospitals A survey of the types of operation carried out is presented in Table 5 from which will be seen that both ovaries had been removed in 13 patients

Fifty six patients received post operative radiation treatment the remaining 4 patients not being referred to us until the diagnosis of a recurrence Roentgen therapy was usually begun 3 to 6 weeks after the operation Factors 200 kV 20 mA FSD 40—80 cm filter 0 5 mm Cu + 1 0 mm Al daily dose 100—400 r (skin dose) one field per day total dose per series 300—2 000 r Particularly the early cases of this series which were referred to us in the twenties and thirties were almost consistently treated with small to moderate

Table 5

Survey of types of operation (60 cases)

	Number of patients
Unilateral oophorectomy	13
Unilateral salpingo-oophorectomy	25
Unilateral salpingo-oophorectomy + resection of contralateral ovary	7
Unilateral salpingo-oophorectomy + hysterectomy	2
Bilateral salpingo-oophorectomy	9
Bilateral salpingo-oophorectomy + hysterectomy	4

Table 3

Duration of symptoms or signs before diagnosis (60 cases)

	Number of patients	Per cent
≤ 1 week	9	15
1 week to 3 months	19	32
4 to 6 months	10	17
7 to 12 months	10	17
≥ 1 year	4	7
Asymptomatic	8	13

correctly diagnosed as having a twisted ovarian tumour or a spontaneous intra abdominal perforation, but it was sometimes impossible to exclude the diagnosis of acute appendicitis before operation.

In one patient pleural effusion was found 11 months before the discovery of the dysgerminoma and in 2 other cases hydrothorax was noticed at the time of the diagnosis of the ovarian tumour. In none of these 3 patients were any other signs of pulmonary involvement present. In one of the patients, however, a metastasis in the supraclavicular region was found. No mention of the presence of ascites in any of these 3 patients was made in the reports of the operations. The frequency of the various presenting symptoms and signs is summarized in Table 2.

Owing to the lack of clear cut and characteristic symptoms in most patients it is extremely difficult to obtain exact data as to the duration of the disease before its diagnosis. An approximate estimation of the duration of the symptoms and signs is, however, possible and, as is seen from Table 3, the progression of the disease is mostly comparatively rapid.

The right ovary was involved in 39 cases, the left ovary in 14, while bilateral involvement was observed in 7. The size of the tumours was in most cases impressive, and some weighing 3 to 4 kg were found. The tumour was adherent to other pelvic organs in 8 patients. Rupture of the tumour before or during the operation occurred in 5 patients, and torsion of the ovarian neoplasm was reported in 2 patients. Ascites was found in 5 patients.

Metastases were noted at the time of operation in 12 patients, in 7 of these bilateral ovarian involvement was evident (bilateral primary tumours or metastasis). Metastases were most commonly found in the omentum, the parametria and the peritoneum. Occasional spread to the lumbo aortic and periportal lymphatics was reported (Table 4).

In the further course a sometimes marked tendency to recurrence and dissemination of the disease was observed. Lymphatic spread was the most common route. Involvement of the retroperitoneal lymph nodes along the iliac vessels and the aorta was usually observed early, but rapid involvement of the epigastric, mediastinal and supraclavicular nodes was also encountered. Haemato

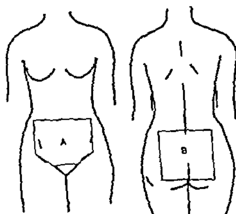


Fig 2 Case 2 Anterior and posterior areas of roentgen irradiation

Normal menstruations February to May 1947 After this time pregnant with confinement in February 1948 Pregnancy and parturition without complications normal child Well at follow up examinations Pregnant for the second time in May 1954 Uncomplicated pregnancy and normal parturition and child No signs of recurrence at repeated follow up examinations Last control September 1960

Case 2 44 year-old nulligravida Primary amenorrhoea Admitted to hospital January 1951 because of attacks of severe abdominal pain The noteworthy observations were a vagina ending in a blind pouch no cervix or uterus and a hard somewhat cystic pelvic mass At operation a grapefruit sized tumour on the left side was extirpated No ovaries or uterus could be found (A detailed report of the sexual abnormalities in this case has been given by MORRIS) Referred to Radiumhemmet in March 1951 At that time no signs of progression of the disease

Roentgen therapy 1951 Field A (400 cm² Fig 2) 15 to 21 March 100 r per day total 600 r and field B (500 cm² Fig 2) 28 March to 3 April 100 r per day total 600 r

At controls completely well up to *April 1953* when a metastasis in the left supraclavicular region was found Roentgen therapy Field C (100 cm² Fig 3) 17 to 22 April 400 r per day total 2 000 r At examination on 6 June 1953 there was no evidence of metastases

Well at control examinations On *15 October 1953* however *a mass over 10 by 15 cm in size* was found in the left upper abdominal quadrant Roentgen therapy Field D (300 cm² Fig 3) 15 to 20 October 150 r per day total 750 r and field F (*125 cm² Fig 3) 21 to 23 October 250* r per day total 750 r No evidence of this tumour was found at examination in December 1953

Severe backache since beginning of *July 1954* At examination at end of month an abdominal mass to the left of the umbilicus was noted Roentgen therapy Field F (150 cm² Fig 3 30 July to 1 August 250 r per day total 750 r

No evidence of the tumour on 1 *September 1954* The patient still had severe backache however as well as difficulties in walking *and urinary* retention Roentgen examination the same day revealed an 8 by 8 cm mediastinal tumour which was displacing the oesophagus a left pleural effusion and partial destruction *of D 11* Roentgen therapy Field A (400 cm²

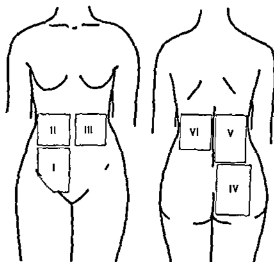


Fig 1 Case 1 Anterior and posterior areas of roentgen irradiation

doses of radiation Later on, however, the treatment was given to each individual patient according to the extent of the disease at the time of operation and the nature of the latter, the clinical findings at the time of institution of roentgen therapy and the further course of the disease In principle two types of initial roentgen treatment were given In most patients of fertile age, in whom unilateral oophorectomy had been performed and in whom there was no indication of dissemination of the disease to the contralateral side at the time of operation or when beginning radiotherapy, no radiation was directed towards the remaining ovary Moderate roentgen doses were given This conservative program was carried out in 20 cases To the remaining 40 patients in whom bilateral oophorectomy had been performed or in whom dissemination of the disease required more extensive radiotherapy, irradiation to the whole pelvis in addition to roentgen therapy to other areas was administered It seems desirable, however, in addition to the above mentioned general conditions, to give detailed data on a few patients who may exemplify various types of roentgen treatment

Case reports

Case 1 24 year old nulligravida No menstrual irregularities Admitted to hospital February 1946 because of pleural effusion Two liters of exudate removed in March subsequent repeat pulmonary roentgen examinations were negative An abdominal mass was found in December 1946 Last menstrual period at the end of that month At operation a month later an encapsulated mass weighing 700 g and originating from the right ovary was removed Unilateral salpingo oophorectomy was performed Referred to Radiumhemmet

Roentgen therapy 27 January to 15 February Three abdominal and corresponding dorsal areas (Fig 1) field sizes varying from 150 to 200 cm² Irradiation given in sequence toward areas I to VI (Fig 1) one field per day three series 150 to 300 r on each occasion total dose 500 to 700 skin r per field No direct irradiation towards the remaining ovary

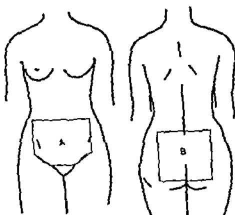


Fig 2 Case 2 Anterior and posterior areas of roentgen irradiation

Normal menstruations February to May 1947 After this time pregnant with confinement in February 1948 Pregnancy and parturition without complications normal child Well at follow up examinations Pregnant for the second time in May 1954 Uncomplicated pregnancy and normal parturition and child No signs of recurrence at repeated follow up examinations Last control September 1960

Case 2 44 year-old nulligravida Primary amenorrhoea Admitted to hospital January 1951 because of attacks of severe abdominal pain The noteworthy observations were a vagina ending in a blind pouch no cervix or uterus and a hard somewhat cystic pelvic mass At operation a grapefruit sized tumour on the left side was extirpated No ovaries or uterus could be found (A detailed report of the sexual abnormalities in this case has been given by MORRIS) Referred to Radiumhemmet in March 1951 At that time no signs of progression of the disease

Roentgen therapy 1951 Field A (400 cm² Fig 2) 15 to 21 March 100 r per day total 600 r and field B (500 cm Fig 2) 28 March to 3 April 100 r per day total 600 r

At controls completely well up to *April 1953* when a metastasis in the left supraclavicular region was found Roentgen therapy Field C (100 cm² Fig 3) 17 to 22 April 400 r per day total 2 000 r At examination on 6 June 1953 there was no evidence of metastases

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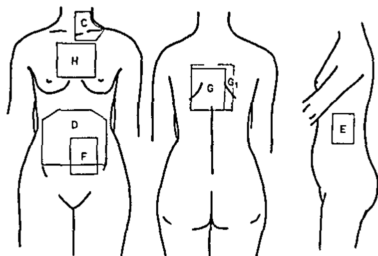


Fig 3 Case 2 Anterior posterior and lateral areas of roentgen irradiation

Fig 2) 4 and 6 September 150 r per day total 300 r field G (200 cm Fig 3) 7 to 13 September 250 r per day total 1 500 r field A (400 cm Fig 2) 15 to 20 September 150 r per day, total 1 050 r and field H (200 cm² Fig 3) 21 to 30 September 150 r per day total 1 200 r Roentgen examination on 27 September showed considerable regress of the mediastinal tumour which had completely disappeared by 7 December 1954 The compression of D 11 remained unchanged up to the last examination on 19 June 1957

Gradual general improvement Started walking by the end of *November 1954* Roentgen *therapy Field G (250 cm Fig 3) 4 to 11 March 200 r per day total 1 400 r*

No signs of recurrence until 2 November 1955 when a metastasis in the left supraclavicular region was noted (cf 17 April 1953) Roentgen therapy field C (100 cm² Fig 3) 2 to 8 November 400 r per day total 2 000 r

At controls afterwards no signs of recurrence was noted The general condition of the patient improved steadily and she walked without difficulty Completely well on 21 October 1960 five years after treatment of the last metastasis

Results of treatment

Fifty six of the 60 patients in the material were referred to Radiumhemmet 5 or more years ago Of these, 13 were admitted 25 or more years ago The observation time for the patients is seen in Table 6

Among the patients treated 5 or more years ago 14 have died from the disease and two have died from other causes (traffic accident and chronic glomerulo *nephritis 8 and 24 years respectively after diagnosis of the disease)* Three patients were lost track of after 7 to 10 years of observation These follow up results imply that the five year survival rate is 75 per cent Among the four patients admitted since 1956 three are well In one a recurrence has been diagnosed

Recurrence was observed rather frequently, in the group surviving 5 years or more this was noted in 15 cases or 36 per cent

Table 6

Time in years after admission for treatment (60 cases)

Years	≥ 25	20—24	15—19	10—14	5—9	3—4	1—2
Number of patients	13	26	33	44	56	58	60
Living	5	12	17	28	37	39	41
Died from the tumour	5	9	11	11	14	14	14
Died from other causes	1	2	2	2	2	2	2

The extent of the disease at the time of operation bears a close correlation to the prognosis A survey is given in Table 7 of the influence of various factors suggesting progression of the disease beyond the ovary at the time of surgical exploration The complications considered here are ascites adhesions or rupture of the tumour and metastases or bilateral involvement of the ovaries For the sake of comparison the patients with the tumour localized to one ovary and without any of these signs of extension have also been included in the table It will be seen that the presence of any of these complicating conditions, with the possible exception of ascites carries a very serious prognosis

The rapidity of the progression of the disease in cases in which radical surgical treatment was impossible or the length of the interval before a recurrence seem to yield considerable prognostic information This is apparent from Table 8 where the time factor as regards progression or recurrence of the disease has been related to the outcome Among the 14 patients who died from the tumour 10 had an almost immediate flaring up or progression of the morbid process after surgical intervention On the other hand half of the surviving patients had their recurrence more than a year after the operation

An analysis of the post operative cour e for these patients may illustrate the effect of radiotherapy as well as the influence of the dose of radiation on the cure rate Table 9 is a summary of the 56 cases treated 5 or more years ago Among these patients 12 were suffering from definite extension of the disease

Table 7

Relation between extension of the disease at the time of operation and prognosis (only cases treated with combined surgery and radiotherapy 5 or more years ago have been included in this table)

Extension of the disease at operation	Number of patients	Five-year survival rate ( )	Recurrence rate (% of living)
Tumour encapsulated and movable	22	95	14
Ascites	5	100	40
Tumour adhesions	8	75	50
Rupture of tumour before or at operation	5	60	0
Metastases (including bilateral ovarian involvement)	12	33	25

Table 8

Relation between rapidity of progression or recurrence of the disease and prognosis (only cases treated 5 or more years ago have been included in this table)

Time interval between operation and progression or recurrence of the disease	Number of patients	Five year survival rate (%)
≤ 2 months	11	9
3 to 6 months	3	33
7 to 12 months	6	66
> 1 year	6	100

beyond the ovary and surgical removal of the tumour was incomplete A further 4 patients were admitted for radiotherapeutic treatment because of recurrence after surgery In 9 of these 16 patients the outcome was fatal In 7 of the patients, however, the cure may be ascribed to the radiotherapy Among the remaining 40 patients there were 13 recurrences, 8 of these have survived for five years or more after the beginning of treatment These results thus show that the present series includes 29 patients who at the beginning of radiotherapeutic treatment or later were suffering from clinical manifestations of the disease The five year survival rate in this group is 52 per cent These results clearly indicate the value of radiotherapy in the treatment of these tumours

From Table 10, however, it is obvious that progression or recurrence of the disease was often noticed in areas previously irradiated The material has been grouped in the table according to the dose of radiation given in the first course of treatment as well as to the incidence of recurrence and its topographical relation to the area of radiation treatment It is seen that low doses of radiation (less than a total dose of 1 500 skin r per area) have a lesser therapeutic effect than higher doses The groups are admittedly small, but the trend seems uniform throughout It is evident that in the majority of cases there was recurrence in areas previously irradiated with low to average doses Increased doses of

Table 9

Incidence of progression or recurrence of the dysgerminoma after the first series of radiotherapy (only cases treated 5 or more years ago have been included in this table)

Extension of the disease at operation	Number of patients	Progression or recurrence	Five year survival rate (%)
A Post operative treatment			
Tumour encapsulated and movable	22	4	95
Ascites adhesions or rupture	18	9	78
Metastases (including bilateral ovarian involvement)	12	9	33
B Not referred until appearance of recurrence after surgery			
Tumour encapsulated and movable	4	2	75

Table 10

Relation between dose of radiation in the first series of treatment and prognosis (only cases treated 5 or more years ago have been included in this table)

Total dose of radiation	Extent of condition at operation	Number of patients	Metastases in radiated area	Metastases in non radiated area only	Five year survival rate (%)
A Post operative treatment					
< 1 500 r per area	Tumour encapsulated and movable	19	2	1	95
	Ascites adhesions or rupture	10	4	2	60
	Metastases (including bilateral ovarian involvement)	8	7	0	12
> 1 500 r per area	Tumour encapsulated and movable	3	1	0	100
	Ascites adhesions or rupture	8	2	1	100
	Metastases (including bilateral ovarian involvement)	4	2	0	75
B Not referred until appearance of recurrence after surgery					
< 1 500 r per area	Tumour encapsulated and movable	2	1	0	100
> 1 500 r per area	Tumour encapsulated and movable	2	1	0	50

radiation cured more than 50 per cent of these patients

Death occurred comparatively early in the fatal cases Nine patients died before the expiration of the first year the remaining 5 patients died within 5 years

Eighteen pregnancies occurred in 10 patients after treatment There were 15 normal babies one interruption of pregnancy on medical indications one abortion and one malformed child

Discussion

Incidence of dysgerminoma Dysgerminoma is a rare tumour In KLAFTEN s material it represented 3 1 per cent of his total ovarian tumours The figure given by NOVAK & GRAY is in the same range SJOVALL, in a considerably larger material of 678 ovarian tumours reported an incidence of only 0 7 per cent whereas SANTESSON (1947) in a series of 707 ovarian neoplasms found 27 pure dysgerminomas thus constituting 3 7 per cent of the total As pointed out by this writer however the material was selected and shows an over representation of tumour cases that are benefited by radiotherapeutic treatment

Its predominant occurrence in young women is clearly borne out by this study This trend is in agreement with most other reports in the literature

(6, 19, 24, 25, 28, 33). The peak of incidence is in the third decade of life. The youngest patient in the series was 8 and the oldest 44 years old.

Genital development and function. The association between dysgerminoma and developmental and sex changes has been emphasized in earlier papers, particularly in those by the pioneer in this field (MEYER). The tumour has often been reported in hermaphrodites and pseudo-hermaphrodites, and in patients with other genital malformations. In the course of time, however, the opinion has gained ground that the majority of dysgerminomas occur in apparently normal women. Thus in a series of 17 patients NOVAK & GRAY found only 3 cases with evidence of malformation of the external or internal genital organs. SJOVALL comes to the same general conclusion as does SANTESSON. In the present series 5 patients had more or less marked developmental anomalies in the genital region. The connection between dysgerminoma and genital malformations does not therefore seem to be as close as was originally presumed.

The signs of normal sexual function found in the majority of the patients of the present series is, on the contrary, impressive. The age at inception of menstruation ranged from 12 to 17 years. Menstruation was normal in most cases and irregularities were only rarely encountered. Thirteen patients had been pregnant before the removal of the tumour. The observation that dysgerminomas are often found in normally fertile women has been repeatedly made (28, 33), although NOVAK & GRAY stated that a large proportion of these patients are sterile both before and after conservative operation. The connection between pregnancy and the diagnosis of the tumour in this series is noteworthy. It was apparent in 7 patients, and in an additional patient a recurrence was observed 6 weeks after the interruption of pregnancy. Such observations have often been made before (3, 4, 8, 13, 37). Whether the state of pregnancy bears any relationship to the development of the tumour, or whether the diagnosis of the tumour in connection with pregnancy is due to the more frequent examinations usually performed in these patients is a matter of conjecture.

The extent of the surgical procedure. Surgery has its given and indisputable place in the treatment of dysgerminoma. There has, however, been discussion on the problem of the radicality of the surgical procedure, i.e. whether bilateral salpingo-oophorectomy should be consistently carried out. When both ovaries are involved in the pathologic process extensive surgery is obviously necessary. FODERL estimated that the tumour appears bilaterally in approximately a third of all cases. PEDOWITZ, FELMUS & GRAYZEL mentioned a somewhat lower figure, in the neighbourhood of 17 per cent. In the present series bilateral involvement occurred in 7 patients or in about 11 per cent. It would therefore seem that the contralateral ovary is apparently normal in 70 to 90 per cent of patients at the time of operation.

As these patients are usually in their second or third decade and therefore in the prime of their reproductive life there has in some quarters been reluctance to recommend radical surgery in cases with an apparently intact contralateral ovary (23 26 28, 33) This attitude has however, lately been strongly criticized by PEDOWITZ et coll In their material of 102 cases in part collected from the literature they found a very high incidence of post operative involvement of the contralateral ovary This occurred in 36 2 per cent of cases in a series of 47 cases of encapsulated dysgerminomas which were adequately followed In an analysis of the end results of attempts to preserve fertility by conservative surgery in 64 cases of dysgerminoma they found that the reproductive function had been retained only in 18 cases In all other cases ovarian function had to be destroyed postoperatively because of recurrence or metastases necessitating roentgen therapy, or a further surgical operation They summarize their experience by stating that conservative surgery performed to preserve fertility is almost always ultimately futile and in view of the high degree of malig nancy of dysgerminoma and the frequency of bilateral involvement, is not warranted PEDOWITZ et coll therefore advocated extensive surgery in every case carried out as bilateral salpingo-oophorectomy and total hysterectomy The rationale for this therapy is according to these authors the great risk of subsequent involvement of the contralateral and at operation apparently normal ovary This great risk is not borne out by the present study In patients who had been subjected to unilateral salpingo-oophorectomy and who had received post operative roentgen treatment dissemination to the remaining ovary occurred in 3 of them or 7 5 per cent

Analysis of certain factors related to prognosis The five year survival rate in the present series is 75 per cent As the series consists of the augmented material of SANTESSON (1947) the percentage is as might be expected in good agreement with his figure as well as with those presented by MATHIEU & PLAUCHU of 66 7 and 63 8 per cent respectively These survival rates are in sharp contrast to those reported by MUELLER TOPKINS & LAPP of 27 3 per cent and by PEDOWITZ et coll of 27 1 per cent It seems of interest to analyze and establish the factors that may possibly have a bearing on this considerable divergence in therapeutic results

A critical examination of differences between the series of patients treated at Radiumhemmet and at most other institutions indicates that the disparity in the results may be mainly due to three factors selection of the patients included in the series the treatment adopted and the routine of follow up examinations

In conformity with the principles applied by SANTESSON only pure dys germinomas have been included in the present study It is evident that this distinction has not been made earlier Apparently most series of dysgerminomas reported have contained both pure dysgerminomas and dysgerminomas with

various structural combinations of other germ cell tumours The considerable difference in the prognosis for pure dysgerminomas and the other less differentiated germ cell tumours has been clearly demonstrated by SANTESSON (1947) and SANTESSON and MARRUBINI (1957) In a review of 17 cases of these latter tumours it was shown (29) that in all patients followed up for a sufficient length of time, i e in 16 patients, the process ran a fatal course within 2 5 to 9 months Of these 17 tumours 5 showed a partly dysgerminomatous structure When dealing with different types of tumours belonging to the same group and showing such definite differences in their response to therapy — from no noticeable effect (less differentiated germ cell tumours) to a considerable response (pure dysgerminoma) — it seems of decisive importance rigidly to isolate the various groups for study Only then can the malignant potential of the pure dysgerminoma be ascertained and a proper evaluation of the gains and risks involved in radical or conservative therapy be possible

The second factor of importance in the attainment of the results at Radiumhemmet seems to be the consistent application of post operative radiotherapy The marked radiosensitivity of the dysgerminoma has been frequently reported (12, 25, 28, 33) Our Case 2 with the successful treatment of the repeatedly appearing metastases at different sites, is an excellent exemple of the susceptibility of the tumour to radiotherapy This is further borne out by the above analysis of the response of recurrences to roentgen treatment in sufficient doses Radiotherapy, however, is not generally adopted in the treatment of dysgerminoma Thus, for instance, in the series of PEDOWITZ et coll only 42 per cent of the patients received post operative roentgen therapy, and no such therapy was given to over 20 per cent of those patients who had recurrence of the disease Of significance seems to be irradiation not only to the region of the removed tumour but also to the para aortic and epigastric lymph nodes This view has been stressed earlier (28, 33)

The third factor of importance seems to be the routine of regular follow up examinations at short intervals after the initial treatment As recurrence usually occurs during the first year after operation (Table 8), and as in spite of a considerable recurrence rate a high five year survival rate has been attained in this series, it appears that the immediate institution of radiotherapy to any metastases is essential

The distribution among a series of patients with a more or less advanced state of the disease will considerably influence the therapeutic results Early diagnosis is a decisive factor As has been shown here, the five year survival rate in patients with the dysgerminoma confined to one ovary and with an intact capsule is 95 per cent, whereas indications of progression of the morbid process beyond the ovary imply a considerably more grave prognosis (Table 7) These results are in line with those of several earlier reports (19, 25, 28)

The age distribution also seems to influence the over all results As seen in Table 1, the five year survival rate is lower in the age groups 10 to 19 years and 40 to 49 years as compared with the age group of 20 and 39 years The former

Table 11

Treatment and prognosis (only cases treated 5 or more years ago have been included in this table)

Treatment	Number of cases	Extent of condition			Five year survival rate (%)	Recurrence rate (% of living)
		Adhesions	Rupture	Metastases**		
Conservative surgery + conservative radiotherapy	17	4	1	2	94	25
Conservative surgery + extensive radiotherapy	23	6	3	7	65	20
Extensive surgery + extensive radiotherapy	12	3	4	3	67	13

* Conservative surgery one ovary completely or partially left extensive surgery both ovaries removed conservative radiotherapy no direct irradiation towards the remaining ovary extensive radiotherapy irradiation to the total pelvis (in addition to other areas see text)
** Bilateral ovarian involvement included

age groups also have a considerably higher rate of recurrence The increased mortality rate in patients before the menarche and after 40 years of age has been noticed earlier (15 25 27)

The extent of combined surgery and radiotherapy On the basis of the results and discussion presented above it seems reasonable to conclude that the combination of surgery and post operative radiotherapy is the method of choice in the treatment of dysgerminoma A point of interest is the evaluation of a possible increase in morbidity and mortality following conservative surgery and radiotherapy as compared with more extensive procedures The problem is whether methods aiming at the preservation of ovarian function are justified or expose these patients to greater risk

Among the 56 patients treated 5 or more years ago surgery was combined with radiotherapy in 52 instances In 40 patients conservative surgery, performed to preserve fertility, was carried out In 23 of these patients the extent of the disease was considered to require a full course of radiotherapy with irradiation to the whole pelvis (as well as epigastric and corresponding dorsal areas) In 17 patients no direct irradiation was given to the remaining ovary Thirteen patients were treated with bilateral oophorectomy and a full course of radiotherapy The hazards and benefits of the different combinations of procedures have been estimated in terms of five year survival rate and frequency of recurrence (Table 11) The frequency of the incidence of rupture of the tumour metastases and evidence of infiltrative growth at the time of operation have also been included in the table It is obvious that the different groups are not the same as regards spread of the morbid process at the beginning of treatment and that they cannot therefore be compared It may, however, be concluded that satisfactory results have been achieved in the group treated with conservative surgery and radiotherapy

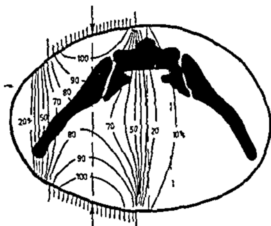


Fig 4 Dose distribution in a pelvis phantom using 200 kV roentgen rays Level of surface LV—SI Transverse diameter 31 cm sagittal diameter 20 cm Size of irradiated areas 10 by 15 cm 20 mA FSD 40 cm filter 0 5 mm Cu + 1 0 mm Al Dotted line 2 6 cm from midline indicates medial limit of left ovary

Genetic effects of conservative radiotherapy Conservative, post operative radiotherapy has been advocated earlier (5, 22, 23), but only single cases have been presented The series from Radiumhemmet contains the largest number of patients that have as far as possible been consistently treated in this way The possible harmful effects caused by this therapy constitute a special problem Although no roentgen treatment is given directly to the remaining ovary, a considerable dose will still reach it by way of secondary irradiation This is clearly recognized at Radiumhemmet, as is also the risk of damage to the hereditary material of the gonad, with transmission of induced mutations to the progeny as a consequence Criticism has been levelled at conservative radiotherapy with this in mind (25) The genetic effects, however, have been referred to in general terms, and no attempt to evaluate, and if possible quantitatively estimate, the genetic harm that may be done to these patients has yet been made It would seem that the special situation of these often very young patients requires a more detailed consideration of the genetic problems involved in conservative radiotherapy

The experimental basis for a discussion on the mutagenic effects of radiation in humans is very scanty Studies of congenital abnormalities in children of American radiologists (1, 14), as well as the extensive genetic study of the effects of the atomic bomb (21, 31) do not present conclusive material for providing direct evidence of the relation between the dose of radiation and the incidence of hereditary traumata in man It has therefore been considered necessary to make an indirect estimate of the minimum radiation dose above which must lie the doubling dose, i e the radiation dose doubling the spontaneous mutation rate (16, 20, 39) The British Medical Research Council (16) considers this dose to be somewhere between 15 and 150 r, whereas the American National Research Council (20) and the United Nations Report (39) give the somewhat more restrictive figures 10 and 100 r

A typical program of conservative treatment is to irradiate 6 areas (cf

Fig 1) As the ovaries are rarely found above a horizontal plane through McBurney s point their distance from the epigastric and corresponding dorsal areas is only exceptionally below 10 to 11 cm A negligible dose will therefore reach the ovaries from irradiation of these areas as compared with the dose obtained from treatment of the contralateral pelvic and corresponding dorsal areas This latter dose has been calculated on the basis of measurements in a tissue equivalent (2) pelvis phantom The isodose distribution is represented in Fig 4 To avoid a possible underestimate of the effect of secondary irradiation the ovary is considered to lie 2 6 cm from a midpoint of the uterus, which is the smallest distance reported (9 11 36) Under these premises approximately 10 per cent of the radiation dose to the pelvic and corresponding dorsal areas will reach the contralateral ovary, or in absolute figures approximately 100 r The same magnitude of dose is arrived at when the calculations are based on the experimental work of KOTTMEIER on the in vivo dose distribution on irradiation of one side

As mentioned above the rather restrictively calculated figure of the American National Research Council (20) and the United Nations Report (39) for the doubling dose is between 10 and 100 r Considering the fairly well established linear relationship between the frequency of induced mutations and radiation dose (35 40) it is reasonable to estimate the dose of radiation reaching the remaining ovary under the conditions of conservative radiotherapy as some where between 1 and 10 times the doubling dose

In order to illustrate possible hereditary effects of this radiation dose it may be assumed that the highest figure calculated above i.e 10 times the doubling dose is a fair estimate The reliability of the information upon which the calculations of the increa ed risk of producing adversely affected descendants have to be based is, of course open to criticism the doubling dose is a hypothetical derivation and the radiosensitivity of the individual genes in the different groups chosen below is probably highly variable It is however possible to obtain a general idea of the effects of increased mutation rates upon the incidence of disease in descendants of radiation exposed patients Furthermore it is evident that the estimations are here based on premises which probably lead to an overestimation of the risk imposed on these patients

The incidence of low grade mental deficiency in the population is approximately 5 per cent (16) The increased proportional risk for a parent exposed to a dose of radiation doubling the causal genes of this defect is 1 5 per cent (16) and in our case consequently 15 per cent The risk of her having a child with low grade mental deficiency is thus increased to approximately 5 9 per cent The risk of bearing psychotic progeny may if the mutation rate in one parent has been doubled be increased by a factor of 0 6 per cent (16) The incidence of manic depressive reactions and schizophrenia has been estimated as 0 53 per cent (39) and the risk for descendants of our hypothetical patient is accordingly increased to 0 56 per cent The phenotype frequency at birth

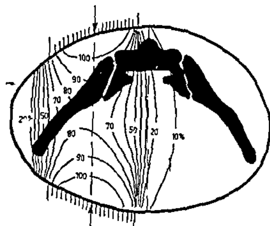


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As the combination of unilateral oophorectomy and conservative radiotherapy is fully justified in certain patients from a medical point of view it appears that removal of the contralateral ovary in these cases is undertaken for the purpose of sterilization and solely for genetic reasons It would therefore seem mandatory in these instances to discuss the benefits and hazards of either procedure with the patient and to pay due attention to her wishes It should be emphasized that from the wider point of view this question of obligation towards future generations to sterilize the radiation exposed patients of this category is not a completely isolated problem If this is to be made a requirement for the radiation treatment of these patients one will definitely be forced to examine critically the permissibility of treating patients with for example severe hereditary metabolic and psychiatric diseases The subsequent child expectancy will thereby be raised for large groups of the population with considerably increased risks of perpetuating these diseases Patients with dysgerminoma are in principle, in the same situation as these other patients, and their dilemma as therapy conditioned potential producers of disabled descendants should be considered in its larger context It is believed that the result will be greater reluctance towards radical methods, when these are not required for medical reasons

Conclusions

The present study has shown the value of post operative radiotherapy in the treatment of dysgerminoma of the ovary It has also clearly demonstrated that conservative surgery combined with conservative radiotherapy is fully justified in certain cases in which preservation of the ovarian function is desired On the other hand an analysis of the relation between the dose of radiation and the prognosis indicates that the small to-moderate doses given in the majority of these cases are sometimes inadequate In most instances there was recurrence in areas irradiated with small doses Intensified radiotherapy cured more than half of these patients

These results necessarily lead to the conclusion that more intense post operative radiotherapy may be desirable The employment of conventional roentgen therapy in larger doses is acceptable in cases in which radiation is given to the whole pelvis But in patients for whom unilateral pelvic treatment is planned this form of therapy will render the preservation of the normal function of a remaining ovary almost impossible Owing to the scatter of the roentgen beam a two- to threefold increase in our small to moderate doses will give the remaining ovary a dose of radiation close to that causing sterilization and in any case an unsatisfactorily large amount from the point of view of genetic consequences The scattering effect may be considerably decreased by using supervoltage radiation and its adaptation to the post operative treatment of dysgerminoma is therefore to be recommended Among the advantage of this type of radiation sharper definition of the beam edge should be

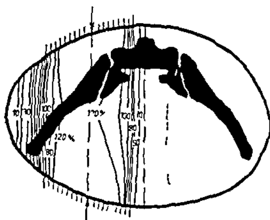


Fig. 5. Dose distribution in a pelvis phantom using cobalt 60 *gamma radiation* given with kilocurie cobalt unit loaded with 4 000 C. Level of surface L V — S I. Transverse diameter 31 cm, sagittal diameter 20 cm. Size of irradiated areas 10 by 15 cm. SSD 80 cm, penumbra trimmer. Dotted line 2.6 cm from midline indicates medial limit of left ovary.

of certain sex linked recessive traits such as *microphtalmus* and *gargoylism* is approximately 12.5 × 10^{-6} (16). The increase in the first generation if mutation rates are doubled in one parent may be estimated as 20 per cent (16). The likelihood of our patient producing babies with these sex linked recessive traits might therefore increase to 37.5 × 10^{-6}. The incidence in the population of certain diseases such as amaurotic idiocy, cerebral diplegia, phenylketonuria and 'true' microcephaly, all probably caused by autosomal recessive genes, is estimated as 0.1 per cent (16). The increased proportional risk for a parent where the mutation rate has been doubled is approximately one half per cent (16), and in our case consequently 5 per cent. The risk of her bearing a child with any of these defects is therefore increased from approximately 0.10 to 0.11 per cent.

The additional risk for further generations of inheriting genetic morbidity or harbouring a disposition for it is almost impossible to estimate. It is realized that the additional risk is perpetuated through an unforeseeable number of generations. Furthermore, it is necessary to bear in mind that the radiation induced mutation process is probably irreversible, and therefore different from spontaneous mutations, where back mutations have been observed (34). On the other hand, it is apparent that, due to dilution and natural selection the chance of inheriting a radiation induced allele is decreased in each generation by at least the factor 1/2 provided the spontaneous mutation rate in the population remains constant.

This matter has been gone into in some detail as a contribution to the discussion of radical treatment with extinction of fertility as against conservative surgical and radiologic treatment in certain cases with preservation of fertility but with certain genetic risks. In the light of the above calculations of the risk involved in unilateral pelvic irradiation, one has to realize that some hereditary damage may be caused. The practical consequences are negligible to society however, and reasonably small to the individual.

As the combination of unilateral oophorectomy and conservative radiotherapy is fully justified in certain patients from a medical point of view, it appears that removal of the contralateral ovary in these cases is undertaken for the purpose of sterilization and solely for genetic reasons It would therefore seem mandatory in these instances to discuss the benefits and hazards of either procedure with the patient and to pay due attention to her wishes It should be emphasized that, from the wider point of view this question of obligation towards future generations to sterilize the radiation exposed patients of this category is not a completely isolated problem If this is to be made a requirement for the radiation treatment of these patients, one will definitely be forced to examine critically the permissibility of treating patients with, for example severe hereditary metabolic and psychiatric diseases The subsequent child expectancy will thereby be raised for large groups of the population with considerably increased risks of perpetuating these diseases Patients with dysgerminoma are, in principle in the same situation as these other patients and their dilemma as therapy conditioned potential producers of disabled descendants should be considered in its larger context It is believed that the result will be greater reluctance towards radical methods, when these are not required for medical reasons

Conclusions

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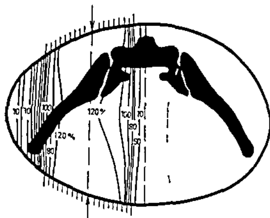


Fig 5 Dose distribution in a pelvis phantom using cobalt 60 gamma radiation given with kilocurie cobalt unit loaded with 4 000 C Level of surface LV — SI Transverse diameter 31 cm sagittal diameter 20 cm Size of irradiated areas 10 by 15 cm SSD 80 cm penumbra trimmer Dotted line 2 6 cm from midline indicates medial limit of left ovary

of certain sex-linked recessive traits such as microphthalmus and gargoylism is approximately $12\ 5 \times 10^{-4}$ (16) The increase in the first generation if mutation rates are doubled in one parent may be estimated as 20 per cent (16) The likelihood of our patient producing babies with these sex linked recessive traits might therefore increase to $37\ 5 \times 10^{-4}$ The incidence in the population of certain diseases such as amaurotic idiocy, cerebral diplegia, phenylketonuria and 'true microcephaly, all probably caused by autosomal recessive genes, is estimated as 0 1 per cent (16) The increased proportional risk for a parent where the mutation rate has been doubled is approximately one half per cent (16), and in our case consequently 5 per cent The risk of her bearing a child with any of these defects is therefore increased from approximately 0 10 to 0 11 per cent

The additional risk for further generations of inheriting genetic morbidity or harbouring a disposition for it is almost impossible to estimate It is realized that the additional risk is perpetuated through an unforeseeable number of generations Furthermore, it is necessary to bear in mind that the radiation induced mutation process is probably irreversible, and therefore different from spontaneous mutations, where back mutations have been observed (34) On the other hand, it is apparent that, due to dilution and natural selection, the chance of inheriting a radiation induced allele is decreased in each generation by at least the factor 1/2 provided the spontaneous mutation rate in the population remains constant

This matter has been gone into in some detail as a contribution to the discussion of radical treatment with extinction of fertility as against conservative surgical and radiologic treatment in certain cases with preservation of fertility but with certain genetic risks In the light of the above calculations of the risk involved in unilateral pelvic irradiation, one has to realize that some hereditary damage may be caused The practical consequences are negligible to society however, and reasonably small to the individual

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mentioned These considerations are illustrated in Fig 5, where it is shown that the amount of radiation reaching the remaining ovary with kilocurie cobalt therapy is only a fraction of that obtained with conventional roentgen therapy (Fig 4) The same effect may, of course, also be achieved with e g the linear accelerator

Acknowledgements

I wish to thank Dr H L Kottmeier and Prof L Santesson for helpful suggestions and constructive criticism Dr T Romanus Department of Forensic Medicine, Karolinska Institutet and Dr A Forssberg Institute of Radiobiology, Karolinska Institutet, for discussion of the genetic part of the paper, and Dr R Walstam Institute of Radiophysics, Karolinska Institutet for advice on certain radiologic aspects of the work

SUMMARY

Sixty cases of dysgerminoma of the ovary treated since 1921 are reported Special attention is paid to the problem of the malignant potential of the tumour and the extent of the therapeutic procedures required The possibility of inducing damage to the hereditary material of a remaining ovary by conservative radiotherapy i e when no direct irradiation falls upon this ovary is discussed in some detail

ZUSAMMENFASSUNG

Der Verfasser berichtet uber 60 Falle mit Ovarialdysgerminom welche seit 1921 behandelt worden sind Besondere Aufmerksamkeit wird dem Problem des malignen Potentials der Tumoren gewidmet sowie dem Ausmass der erforderlichen therapeutischen Massnahmen Die Moglichkeit dass ein ubriggebliebenes Ovarium nach konservativer Radiotherapie d h wenn keine direkte Bestrahlung des Ovariums vorkommt der Erbmasse einen Schaden zu fuhren konne wird eingehend besprochen

RÉSUMÉ

L auteur présente soixante cas de dysgerminome de l ovaire traités depuis 1921 Il a étudié particulièrement le problème du potentiel malin de cette tumeur et l importance des moyens thérapeutiques qu elle nécessite Il examine de façon assez détaillée la possibilité de lésion du matériel héréditaire de l ovaire restant par la radiothérapie quand cet ovaire n est pas exposé à l irradiation directe

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FROM THE DEPARTMENT OF RADIATION THERAPY (DIRECTOR WALTER T MURPHY) AND THE DEPARTMENT OF MEDICINE B (DIRECTOR JOSEPH E SOKAL), ROSWELL PARK MEMORIAL INSTITUTE BUFFALO, NEW YORK U S A

EVALUATION OF CYREN B AS A LEUKOCYTE PROTECTING AGENT IN PATIENTS UNDERGOING RADIOTHERAPY OR CHEMOTHERAPY FOR MALIGNANT LYMPHOMA

by

JOHN H WEBSTER ELLEN M LESSMANN and JOSEPH E SOKAL

A limiting factor in the radiation therapy and chemotherapy of malignancy is the leukopenia resulting from such treatment, which sometimes necessitates the interruption of therapy before a desired dose has been given In the past innumerable compounds have been used in an attempt to treat this com plication and none has been found to be clinically useful In a recent report BELLESIA LUSVARGHI PASQUINELLI and DARDARI (1957) claimed to have largely solved this problem by the use of diethyldioxystilbenedipropionate This agent was selected for clinical trial after basic studies had indicated that estrogens of this type might increase the resistance of leukocytes to several types of injury (PEDERZINI et coll 1955 and STORTI and PEDERZINI 1955) The conclusions of the clinical study were that this drug possessed a marked ability to prevent or ameliorate leukopenia induced by radiotherapy or nitrogen mustard therapy There was no apparent interference with the therapeutic effects of either form of treatment

Because of the desirability of confirming such an effect if possible it was decided to test this drug in a well controlled study, using a series of patients treated by techniques which would usually induce leukopenia

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Table 1

Method of classification of patients into "high risk" and "low risk" groups with respect to bone marrow depression

I Previous therapy during the past two years	
1 One course of nitrogen mustard and/or irradiation of peripheral nodes only	Score 0
2 Two courses of nitrogen mustard or one course of irradiation to the midline trunk	Score 1
3 More than two courses of nitrogen mustard or more than one course of irradiation to the midline trunk	Score 2
II Bone marrow status	
1 Normal marrow	Score 0
2 Possibly depressed granulocytic elements	Score 1
3 Definite depression of granulocytic elements	Score 2
III Incidence of leukopenia during previous therapy	
1 Nitrogen mustard or irradiation of the midline trunk	
a No leukopenia	Score 0
b Leukocyte count between 3 000 and 5 000/mm³	Score 1
c Leukocyte count below 3 000/mm³	Score 2
2 Irradiation of peripheral nodes only	
a No leukopenia	Score 0
b Leukocyte count below 5 000/mm³	Score 2

Total score = Score I + Score II + Score III

Classification

Unlikely to develop leukopenia	Total score 0—2
Very likely to develop leukopenia	Total score 3—6

Materials and methods The effect of diethyldioxystilbenedipropionate (Cyren B, Bayer) was assessed in 67 patients with malignant lymphoma treated either with nitrogen mustard, 0 4 mg/kg body weight divided into four daily doses, or with radiation directed to the mediastinal or retroperitoneal areas Because many of these patients had had previous courses of irradiation or chemotherapy and may have had varying degrees of bone marrow depression, they were subclassified into two groups before treatment was started, i e those more, and those less likely to develop leukopenia This subclassification was based on the selection method described in Table 1 Patients with pre existing leukopenia were excluded from this study Patients were allocated to treatment and control groups according to a table of random numbers The distribution of patients among the various treatment and control groups is shown in Table 2

Cyren B, 2 5 mg/ml in sesame oil, was administered intramuscularly in individual doses of 2 5 mg according to the following schedules

1 Those patients undergoing nitrogen mustard therapy received daily injections starting the day before the first dose of nitrogen mustard and ending

Table 2

Distribution of patients among various study groups

	Nitrogen mustard		Radiotherapy	
	Treatment group	Control group	Treatment group	Control group
High risk	5	8	9	10
Low risk	7	7	9	12
Total (67)	12	15	18	22

the day of the fourth dose a total of 12 5 mg of the drug being given in five days

2 Those patients undergoing radiation therapy received injections of the drug three times weekly when their course of radiotherapy extended over a period shorter than four weeks or every third day when their course of radiotherapy extended over a period longer than four weeks Therapy with the drug was instituted when the accumulated tumor dose had reached 750 rads

Hemoglobin and hematocrit determinations leukocyte count and platelet count were obtained at least twice before treatment Upon the institution of radiotherapy or chemotherapy, leukocyte and platelet counts were obtained three times weekly and hemoglobin and hematocrit determinations were made weekly These observations were continued throughout the entire course of therapy and for a minimum of four weeks thereafter

Evaluation of response Leukopenia was evaluated at two levels i e depression of the white blood cell count below 5 000 and below 3 000 per mm³ This was done because of the possibility that a therapeutic effect might be manifested by prevention of severe leukopenia even though mild leukopenia occurred and because patients with slight leukopenia might respond differently from those with a more profound leukocyte depression White blood cell counts were graphed individually for each patient The areas enclosed by

Table 3

Incidence of leukopenia and thrombocytopenia among the study groups

Patient category	No of cases	WBC below 5 000 mm	WBC below 3 000 mm	Pl below 150 000 mm³	Pl below 100 000 mm
Control high risk irradiated	10	10	6	6	2
Cyren B high risk irradiated	9	7	4	6	4
Control low risk irradiated	12	10	3	6	2
Cyren B low risk irradiated	9	5	4	4	1
Control high risk HN_2 treated	8	7	7	7	6
Cyren B high risk HN_2 treated	5	4	3	3	2
Control low risk HN_2 treated	7	6	5	5	3
Cyren B low risk HN_2 treated	7	7	4	4	2
Total	67	56	36	41	22

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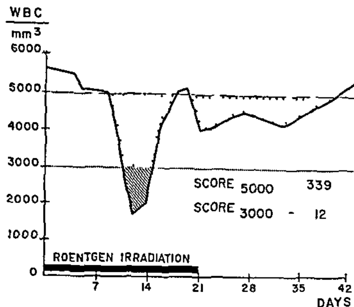
Results of statistical analysis of leukopenia scores of Cyren B treated and control patients

Classification	Mean leukopenia scores ± S E. Controls	Cyren B treated	x^2	t	P
Nitrogen mustard					
High risk,					
WBC below 5 000	29 97 ± 8 42	13 37 ± 7 11	0 18	1 9[illegible]	0 20>P>0 10
WBC below 3 000	7 29 ± 3 43	0 88 ± 0 45	0 07	1 23	0 30>P>0 20
Low risk					
WBC below 5 000	3[illegible] 80 ± 15 98	14 4 ± 4 57	0	1 17	0 30>P>0 20
WBC below 3 000	3 97 ± 1 82	2 86 ± 1 71	0	0 51	0 50>P>0 30
Roentgen irradiation					
High risk					
WBC below 5 000	34 10 ± 9 43	32 99 ± 16 32	0 82	0 [illegible]8	0 50>P>0 30
WBC below 3 000	3 94 ± 2 76	9 97 ± 7 79	0 05	0 26	0 70>P>0 50
Low risk					
WBC below 5 000	14 85 ± 3 60	14 77 ± 6 35	0 82	0 26	0 70>P>0 50
WPC below 3 000	0 37 ± 0 35	0 99 ± 0 61	0 2[illegible]	0 92	0 50>P>0 30

The value of P is associated with the value for t since this was considered the most sensitive test

sensitive rank t test (Bross 1954 Wilcoxon 1945) for analysis of the differences in leukopenia and thrombocytopenia scores Both tests failed to demonstrate a beneficial effect of the drug The values derived from the application of these tests in the analysis of the leukopenia scores are presented in Table 4 The large standard errors seen in this table are due to the great variation in scores among the individuals comprising each group The high risk and the low risk patients in each category were then combined in order to increase the size of the control and treatment groups and statistical analysis was repeated using the Chi square test Again no significant advantage of treatment with Cyren B was seen While a slight advantage due to a real action of Cyren B cannot be excluded for the nitrogen mustard group these results indicate that this drug does not confer important protection against leukopenia or thrombocytopenia

A by product of this study was the opportunity afforded us to evaluate our criteria for assigning patients to high risk and low risk groups with respect to the hazards of inducing leukopenia and thrombocytopenia Comparison of the course of control patients in the high risk and low risk groups revealed a difference of borderline significance ($0 10>P>0 05$) in roentgen irradiated patients with respect to leukopenia The criteria listed in Table I proved to have no predictive value for nitrogen mustard treated patients or for roentgen irradiated patients insofar as thrombocytopenia was concerned Since no significant difference was found between the control and the Cyren B treated patients these groups were combined and analysis of the differences between high risk and low risk patients was repeated The significance of the dif



Graph representing the white blood cell count of a roentgen irradiated patient and the determination of the leukopenia scores Both the stippled and striped areas are included in the leukopenia score below 5 000 while only the striped area is included in the leukopenia score below 3 000

that part of the white blood cell curve below the line for 5 000 (or 3 000) cells per mm³ expressed both the severity and the duration of leukopenia A representative graph of this type is given A numerical "leukopenia score" which was the product of the amount of depression of the leukocyte count below 5 000 (or 3 000) per mm³, multiplied by the number of days that such depression persisted, was determined for each patient Thrombocytopenia was evaluated in a similar fashion, using 150 000 and 100 000 platelets per mm³ as the limiting lines Cyren B treated patients were then compared with the appropriate control groups, using both the Chi square test and the rank-t test for analysis of differences in leukopenia and thrombocytopenia scores

Results and Discussion

The incidence of leukopenia and thrombocytopenia encountered during or after the treatment of these 67 patients is shown in Table 3 From this table it is apparent that hematologic depression occurred frequently enough to provide a sample for evaluation, since the great majority of patients developed leukopenia and slightly over half, severe leukopenia It also can be seen that there is no marked difference between the control and the Cyren B treated groups In the latter, three fourths of the patients developed leukopenia and half, severe leukocyte depression

For more precise evaluation, each group of Cyren B treated patients was compared with its control group, using both the Chi square test and the more

Table 4

Results of statistical analysis of leukopenia scores of Cyren B treated and control patients

Classification	Mean leukopenia scores ± S. E. Controls	Cyren B treated	x	t*	P*
Nitrogen mustard					
High risk					
WBC below 5 000	29 97 ± 8 42	13 37 ± 7 11	0 18	1 92	0 20>P>0 10
WBC below 3 000	7 29 ± 3 43	0 88 ± 0 45	0 07	1 23	0 30>P>0 20
Low risk					
WBC below 5 000	39 80 ± 15 98	14 4 ± 4 57	0	1 17	0 30>P>0.20
WBC below 3 000	3 97 ± 1 82	2 86 ± 1 71	0	0 51	0.50>P>0 30
Roentgen irradiation					
High risk					
WBC below 5 000	34 10 ± 9 43	32 99 ± 16 32	0 87	0 78	0 50>P>0 30
WBC below 3 000	3 94 ± 2 76	9 97 ± 7 79	0 05	0 26	0 70>P>0 50
Low risk					
WBC below 5 000	14 85 ± 3 60	14 77 ± 6 35	0 82	0 26	0 70>P>0 50
WBC below 3 000	0 37 ± 0 35	0 99 ± 0 61	0 22	0 92	0 50>P>0 30

The value of P is associated with the value for t since this was considered the most sensitive test

sensitive rank t test (BROSS 1954 WILCOXON 1945) for analysis of the differences in leukopenia and thrombocytopenia scores Both tests failed to demonstrate a beneficial effect of the drug The values derived from the application of these tests in the analysis of the leukopenia scores are presented in Table 4 The large standard errors seen in this table are due to the great variation in scores among the individuals comprising each group The high risk and the low risk patients in each category were then combined in order to increase the size of the control and treatment groups and statistical analysis was repeated using the Chi square test Again no significant advantage of treatment with Cyren B was seen While a slight advantage due to a real action of Cyren B cannot be excluded for the nitrogen mustard group these results indicate that this drug does not confer important protection against leukopenia or thrombocytopenia

A by product of this study was the opportunity afforded us to evaluate our criteria for assigning patients to high risk and low risk groups with respect to the hazards of inducing leukopenia and thrombocytopenia Comparison of the course of control patients in the high risk and low risk groups revealed a difference of borderline significance (0 10>P>0 05) in roentgen irradiated patients with respect to leukopenia The criteria listed in Table 1 proved to have no predictive value for nitrogen mustard treated patients or for roentgen irradiated patients insofar as thrombocytopenia was concerned Since no significant difference was found between the control and the Cyren B treated patients these groups were combined and analysis of the differences between high risk and low risk patients was repeated The significance of the dif

ferences was not increased It is apparent that our criteria for assessing the risks of leukopenia and thrombocytopenia need considerable improvement

Acknowledgement

We wish to thank Dr I D J Bross for his help with the statistical evaluation Diethyl dioxystilbenedipropionate was kindly supplied by *Farbenfabriken Bayer Aktiengesellschaft* Leverkusen, Germany and is available in that country as Cyren B

SUMMARY

The alleged protective effect of diethyldioxystilbenedipropionate (Cyren B) against radiation or nitrogen mustard induced leukopenia was investigated in 67 patients with malignant lymphoma The patients were randomly allocated to treatment and control groups and appropriate statistical techniques were used to determine whether this drug afforded any significant protection No protective action of the drug against leukopenia or thrombocytopenia was seen The authors were unable to predict the likelihood of developing thrombocytopenia or leukopenia in the individual patient about to undergo treatment

ZUSAMMENFASSUNG

Der angenommene Schutzeffekt des Diethyldioxystilbenedipropionates (Cyren B) gegen Leukopenie, welche durch ionisierende Strahlung oder Stickstoff Senfgas hervorgerufen wird, ist bei 67 Patienten mit malignem Lymphom untersucht worden Die Patienten wurden willkurlich einer Behandlungsgruppe bzw einer Kontrollgruppe zugeteilt und geeignete statistische Methoden wurden benutzt um festzustellen ob diese Droge irgendeinen signifikanten Schutz erbot Keine schutzende Eigenschaft der Droge gegenuber der Leukopenie oder Thrombocytopenie wurde beobachtet Die Autoren waren nicht in der Lage die Wahrscheinlichkeit eines Zustandekommens einer Thrombocytopenie oder Leukopenie bei den in Behandlung befindlichen individuellen Patienten vorauszusehen

RÉSUMÉ

Le prétendu effet protecteur du dipropionate de diéthyldioxystilbène (Cyren B) contre la leucopénie induite par les radiations ou les moutardes azotées a été étudié sur 67 malades atteints de lymphome malin Les malades ont été répartis au hasard en groupes traités et groupes témoins et on a utilisé des techniques statistiques appropriées pour déterminer si ce produit donne une protection significative On n a constaté aucune action protectrice de ce produit contre la leucopénie ou la thrombocytopénie Les auteurs n ont pu prévoir l apparition vraisemblable d une thrombocytopénie ou d une leucopénie chez les malades qui allaient être soumis à ce traitement

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FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR ASSOC PROF KURT LIDÉN), UNIVERSITY OF LUND SWEDEN

CESIUM 137 BURDENS IN SWEDISH LAPLANDERS AND REINDEER

by

KURT LIDEN

We measured the Cs 137 burdens in a group of Norwegians in October 1960 and found them to be several times higher than a normal control group drawn from the population of Lund Sweden In January 1961 a group of 15 subjects from Oslo and 6 from Bergen in Norway were measured in our whole body counter at Lund The Oslo group showed an average Cs 137 burden of 21 nc and 180 pc/g K with a maximum value of 32 nc, 340 pc/g K and the Bergen group an average of 60 nc 480 pc/g K with a maximum of 106 nc 810 pc/g K (BAARLI LIDEN MADSHUS and MCCALL 1961) These values were partly a result of a goat s milk cheese diet, a Cs 137 content of goat s milk cheese as high as 41 nc/kg is reported from Norway

We became interested in other groups in Scandinavia with unusual diets We measured a sample of commercially available reindeer meat from an unidentified source in northern Sweden and found it to contain 28 nc/kg while beef from the Lund area showed less than 0 1 nc/kg It was thus obvious that the people in northern Sweden on a reindeer meat diet particularly the Laplanders must have substantially higher Cs 137 burdens than other Swedes We measured a Laplander studying in Lund (code No 107) in March 1961 and found that he showed 196 nc Cs 137 During the previous two years he had spent most of his time in Lund and had therefore only occasionally eaten

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Table

Cs 137 and potassium content of three Laplanders and one subject from Lund

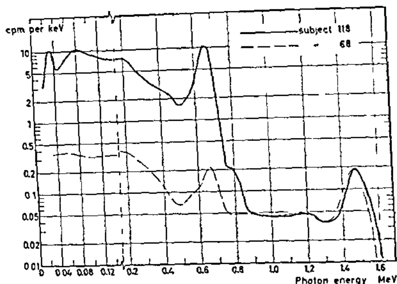
Code No	Sex	Age years	Weight kg	Cs 137 nc	K g	Cs 137/K pc/g	Diet R = reindeer meat G = goat cheese
107	M	35	67	196	97	2 020	R occasionally G 20—50 g/day
118	M	46	52	361	107	3 360	R 200—400 g/day no G
119	F	34	56	242	90	2 690	R 200—300 g/day no G
68	M	23	57	5 9	98	60	no R, no G

reindeer meat, but he had had goat's milk cheese regularly, the Cs 137 content of which we found was high His Cs 137 pattern was thus not to be one of pure reindeer meat In order to prove the effect of a predominantly reindeer meat diet two reindeer raising Laplanders from latitude 66 6° N were also measured (at the beginning of May 1961) in our iron room (code Nos 118 and 119) The result of the three Laplanders studied is given in the Table above For comparison, data for a subject in the control group of Lund are also given Cases 118 and 119 show a Cs 137 activity 45 and 30 times as high as the average of 8 0 nc of the local control group of Lund and 3 4 and 2 3 times as high as the highest value in the Norwegian group mentioned above

The spectrum of case 118 is shown in the figure Above 150 keV it was obtained with a 5 diam × 4 thick NaI(Tl) crystal at 25 keV per channel with the subject in the Argonne chair geometry, below 150 keV a thin crystal assembly with two 110 mm diam × 5 mm thick NaI(Tl) crystals in parallel was used (LIDEN and MCCALL 1961) The Ba $K\alpha$ roentgen line at 32 keV is easily identified This may be the first time that this line has been observed and identified in the spectrum of a normal human being There is also a bump in the high energy slope of the 0 662 MeV peak, the origin of which is not obvious, a small body burden of (Zr + Nb) 95 may be a possible explanation This bump is slightly more marked in the reindeer meat spectrum The matter is being further studied

Measurement of reindeer meat produced in the area where cases 118 and 119 are living gave a Cs 137 content of 24 nc/kg The Cs 137 activity in adult reindeer is probably of this order of magnitude in most parts of Scandinavia

If the daily intake of meat is known, the body absorption of Cs 137 from the gastro intestinal tract may be calculated Using a biologic half life for Cs of 74 days, obtained from an intravenously injected subject of the same age as case 118 and studied in Lund for 7 months, the excretion ought to be 0 94 % per day and thus, if equilibrium exists, the intake must be the same If Cs 137 is taken in from reindeer meat only, 300 g a day corresponds to about 7 nc



Spectrum of a Swedish Laplander with a Cs 137 burden of 361 nanocurie (code No 118) and a subject from Lund with a Cs 137 burden of 5 9 nc (code N 68). Above 0 15 MeV the spectrum is measured with a 5 diam × 4 thick NaI(Tl) crystal at 25 keV per channel below 0 15 MeV two 110 mm diam × 5 mm thick NaI(Tl) crystal in parallel have been used at 4 keV per channel The measurements are made in Argonne chair geometry Both subjects contain approximately the same amount of potassium 107 g and 98 g respectively

Cs 137 the measured Cs content of 361 nc in case 118 then corresponds to an absorption of roughly 50 % of the Cs 137 introduced orally This figure will be studied more carefully using the reindeer meat as a naturally labelled substance

A Cs 137 content of the soil of 14—42 nc per m² is reported from Sweden at latitude 63 N (LOW and EDVARSON 1960) Other parts of Sweden show 18—26 nc/m² with an average in both cases of 20 nc/m² The explanation of the high Cs level in reindeer is very likely to be found in their habit of grazing on lichens and herbs over large areas of ground we have measured Cs 137 activities in lichens of 10 to 30 nc/kg The reindeer food and its metabolism have to be studied in more detail before any relation between food activity and meat contamination can be established

According to the recommendations of ICRP the maximum permissible body burden of Cs 137 is 3 0 μc for people outside controlled areas Thus the Cs 137 activity in case 118 is about one tenth of this value giving a yearly dose contribution of roughly 55 mrad which is about three times the internal potassium dose and 50 % of the average human dose from natural sources of radiation in Sweden 100 mrad per year

The dose contribution from other internal sources is mainly due to (Sr + Y)

90 Attempts to determine this activity by external measurements with our thin crystal method (LIDEN and McCALL 1961) are now being undertaken Our minimum detectable amount is at present 20 nc Y 90 if the effect of the bodyweight on the background and on the Cs 137 spectrum is accurately known This requires further studies in the present case

The number of Laplanders in Sweden is about 10 000, there are 20 000 in Norway, 3 000 in Finland, and 2 000 in Russia According to HYRENIUS (1961) the reindeer raising Laplanders in Sweden constitute a group of about 2 600 people, who thus may have Cs 137 burdens similar to the values given above No groups of subjects of comparable size and activity level have previously been reported Extensive studies of the Swedish group will be undertaken by us and by other research institutes in Sweden However, it is easy to see that groups of people with living habits similar to the Laplanders do exist in other countries It is desirable that some of them should also be studied

SUMMARY

Measurements in the whole body counter at Lund have shown the Cs 137 burden in Swedish Laplanders to be 20 to 40 times as high as in a control group of Lund A diet of reindeer meat containing about 25 nc Cs 137 per kg is the main source of this unique Cs 137 level in human subjects

ZUSAMMENFASSUNG

Messungen mit dem Ganzkorperzahler in Lund haben gezeigt dass die Cs 137 Aktivitat der schwedischen Lappen 20 bis 40 mal grosser ist als die Aktivitat einer Kontrollgruppe in *Lund Tagliche Kost mit reichlichen Mengen von Renntierfleisch mit einer Aktivitat von* etwa 25 nc Cs 137/kg ist die Hauptursache fur diesen einzigartigen Cs 137 Gehalt im Menschen

RÉSUMÉ

Des mesures effectuées avec le compteur pour le corps entier de Lund ont montré que la charge en Cs 137 de Lapons suédois est de *20 à 40* fois supérieure à celle d un groupe témoin de Lund l alimentation à la viande de renne contenant environ 25 nc de Cs 137 par kg e t la principale source de ce taux unique en Cs 137 chez l homme

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RESPIRATORY KYMOGRAPHY IN SILICOSIS

by

NILS P G EDLING and SAM SCHMIDT

The diagnosis of silicosis will demand a careful assessment of the amount of work the patient is able to perform and this may be said to bear a direct relationship to the capacity of the lungs This capacity will be reduced by any decrease in the functioning alveolar space in the areas of the lungs affected During the entire course of the disease and specially during the fibrotic stage with severe shrinkage the densities are generally localized to the upper zones of the lungs Breathing will consequently become more and more dependent on the lower parts of the lungs and the diaphragm will gradually take over the main part of the respiration At the same time secondary emphysema in the basal zones will further decrease the respiratory capacity

A study of the diaphragmatic and costal movements is important in the assessment of the breathing capacity Fluoroscopy can give a general idea of the excursions of the diaphragm but by means of roentgen kymography it is possible to obtain an objective record of the respiratory movements of both the diaphragm and ribs

The literature on roentgen kymography in silicosis is scanty DI LAURO & DI GUGLIELMO (1950) reported 12 cases in which they investigated the morphology symmetry and synchronism of the diaphragmatic movements as well as the synchronism of the diaphragmatic in relation to the costal movements

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From Roentgendiagnostic Department B (Director Docent N P G Edling) Karolinska Sjukhuset Stockholm Sweden Submitted for publication 24 March 1961



Fig 1 Lungs silicosis stage III Asymmetric distribution of densities Confluent infiltrations in upper zone of right lung emphysema flattened diaphragm

They noticed no abnormality regarding these points and made no mention of the amplitude of the diaphragmatic or costal movements NAUMOW (1959) published roentgenkymographic studies in pneumoconiosis without illustrations and found no direct relationship between the morphologic appearances and changes in function In his opinion dysfunction of the respiration, as shown by protracted expiration and deformation of the diaphragmatic waves, was caused by tuberculosis and not by pneumoconiosis His conclusion was that roentgen kymography cannot be considered a useful method in the early diagnosis of pneumoconiosis

We present a series of cases of silicosis, diagnosed clinically and roentgenologically and examined by roentgen kymography of the respiratory movements of the diaphragm and ribs

Material and Methods The material comprises 25 cases examined with the kymographic technique described by SCHMIDT (1960) Of these, 4 cases were classified as stage I, 4 as stage II and 17 as stage III of silicosis In the last

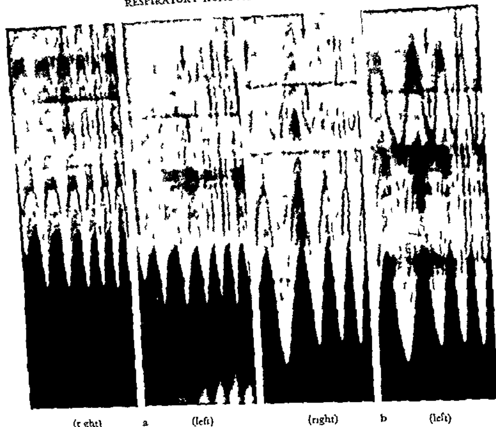


Fig. 2. Same case as in fig. 1. Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration. Normal waveform. Normal amplitude of diaphragmatic waves. Markedly reduced amplitude of costal waves (arrows).

group two of the cases had active and two inactive tuberculosis associated with the silicosis.

The kymographic examination was performed in the supine position. The kymograph contains two movable lead plates with a 1 mm wide and 50 cm long slit in each. Each slit is placed under fluoroscopic control over one side of the diaphragm and lower part of the chest about 2 to 4 cm medial to the lateral thoracic wall and parallel to the long axis of the body. Two 30 × 40 cm films are placed in the moving tray and exposed, one during ordinary and one during deep respiration. The exposure time is 20 seconds. We obtain a record of the movement of a one millimetre broad segment of the diaphragm and the lower part of the chest on each side. The posterior parts of the 7th to the 10th ribs are usually recorded. The movements of the anterior parts of the

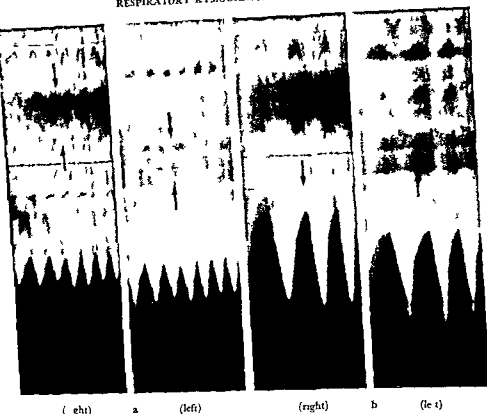


Fig 1 Lungs silicosis stage *III* Asymmetric distribution of densities Confluent infiltrations in upper zone of right lung emphysema flattened diaphragm

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(right) a (left) (right) b (left)

Fig 4 Same case as in fig 3 Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration Normal waveform Slightly reduced amplitude of diaphragmatic waves Very small amplitude of costal waves (arrows)

more small inspiratory movements unilaterally in 4 cases (Figs 5 and 6) and bilaterally in 3 cases These last 7 cases belonged to stage III group

The amplitude of the diaphragmatic waves was within normal limits in 8 cases (Figs 1 and 2) increased in 9 (Figs 5 6 7 and 8), and reduced in 8 cases (Figs 3 and 4) In 6 of these last 8 cases with exception of the one illustrated the difference of amplitudes in ordinary and deep respiration was small and in the two remaining cases there was no difference Disturbances in the respiratory diaphragmatic amplitude occurred in all stages of the disease As many as 11 of the 17 cases belonging to stage III had ordinary or increased diaphragmatic amplitudes

A difference of amplitude between right and left sides was observed in some cases (Figs 3 4 7 and 8) this difference did not exceed 0 5 cm which is a normal finding There was no correlation between the differences in amplitude on the right and left sides and differences in the radiologic appearances of



Fig 3 Lungs silicosis stage III Fairly symmetric distribution of densities Confluent infiltrations in upper medial parts of lungs shrinkage and emphysema The diaphragm is slightly flattened

ribs are usually not recorded and the description of the costal movements in this paper therefore refers to the posterior parts of the ribs

The normal kymographic tracing of the diaphragmatic movements is a regular, slightly asymmetric, steep wave The ascending limb corresponds to expiration, the descending one to inspiration The asymmetry is caused by a slight retardation of the movement near the end of expiration The average amplitude in normal cases is 2 cm in ordinary, and 4 5 cm in deep breathing

The normal kymographic tracing of the costal movements is a regular and slightly asymmetric but flat wave, whose direction is opposite to that of the diaphragmatic wave Thus the descending limb corresponds to expiration, the ascending one to inspiration The average amplitude in normal cases is 1 to 2 mm in ordinary, and 3 to 5 mm in deep breathing

Results

The form of the diaphragmatic waves in the kymogram was normal in 18 cases (Figs 1 to 4) The form was abnormal during expiration due to one or

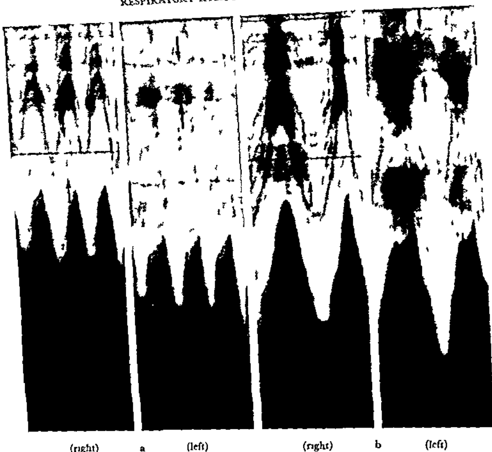


Fig 6 Same case as in fig 5 Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration Normal diaphragmatic waveform on right side Small inspiratory movements at the end of expiration on the left side Amplitude of diaphragmatic waves moderately increased in deep respiration No costal movements on right side normal amplitude on left side (arrows)

form or amplitude between the 4 cases which had tuberculosis associated with silicosis and the other cases

Discussion and conclusions

The three different stages of silicosis are represented in our series of 25 cases The majority were classified as stage III and about half of these had advanced fibrotic changes

According to the results the silicotic changes in the lungs in the majority of the cases did not influence the form of the kymographic waves of the diaphragm and ribs A minority of the cases had a slightly irregular expiration



Fig 5 Lungs silicosis stage III Fairly symmetric distribution of densities Shrinkage in upper and middle zones on both sides emphysema Diaphragm normal

both lungs, when present No paradoxical movements of the diaphragm were observed

The form of the costal waves is generally difficult to assess due to the small amplitude and superimposed structures In all probability the abnormal wave form in the diaphragmatic tracing which occurred in some cases was represented in the costal tracing but, with one exception (Figs 5 and 6), was too small to be discernible

The amplitude of the costal movements was average in 7 cases (Figs 7 and 8), increased on one side in 2, and reduced in 8 cases (Figs 1, 2, 3 and 4) No appreciable costal respiration was evident on either side in 4 cases or on one side in another 4 cases (Figs 5 and 6) In one of the seven cases with average amplitude the costal movements were paradoxical, for this we have no satisfactory explanation

There was no constant relationship between the disturbances in the diaphragmatic and costal movements and the various stages of silicosis It may also be noted that there was no appreciable difference observed in the wave

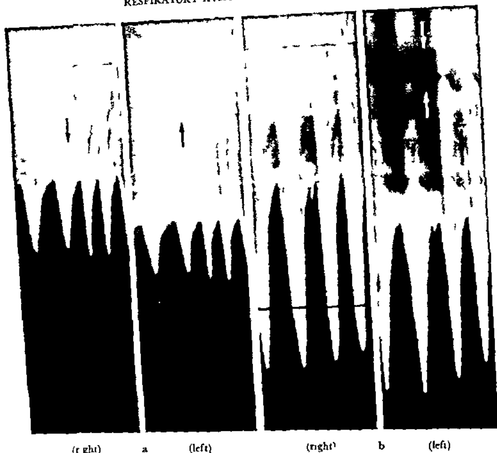


Fig 8 Same case as in fig 7 Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration Abnormal form of occasional waves due to small inspiratory movements at the end of deep expiration Markedly increased amplitude of diaphragmatic waves in deep respiration Normal amplitude of costal waves (arrows)

reduction of the respiratory capacity in the upper parts of the thorax due to the fibrotic changes these parts of the lungs, normally ventilated mainly by costal movements were therefore more or less not functioning The deficient costal respiration was compensated by the diaphragmatic respiration This would confirm the relationship between costal and diaphragmatic breathing in the compensatory mechanism

It would appear that respiratory kymography may be used as a qualitative functional test for evaluation of the respiratory capacity of a patient Moreover it may also be valuable from the therapeutic point of view As in emphysema due to other causes the treatment of emphysema in silicosis with respiratory exercises varies with the individual type of respiratory deficiency The result of treatment may also be followed by means of kymography



Fig 7 Lungs silicosis stage III Asymmetric distribution of densities Confluent infiltrations in upper lateral part of right lung Shrinkage and emphysema flattened diaphragm

phase This is in no way a characteristic finding in silicosis as it also occurs in other pulmonary conditions This indicates that lung changes due to silicosis do not generally affect the form of the breathing mechanism

The amplitude of the diaphragmatic respiratory movements was average or increased in nearly three quarters of the cases, and moderately reduced in the rest This shows that the diaphragmatic function is usually not impaired in silicosis, even when advanced pulmonary changes are present On the contrary, the relatively large number of cases with increased diaphragmatic amplitude would suggest that a compensatory mechanism for the reduced respiratory capacity of the damaged lung tissues often develops It also suggests that the emphysematous component of the functioning part of the lungs is not very large, as the pulmonary tissues are capable of great volume changes When the amplitude was reduced this with a few exceptions, occurred only in deep respiration and was of moderate degree

In some of the cases the diaphragm was more or less flattened without constant relationship to its amplitude This change in the shape of the diaphragm does not therefore in itself indicate impairment of the movements

The amplitude of the costal movements was in the majority of the cases reduced or absent The impaired costal respiration may be explained by the

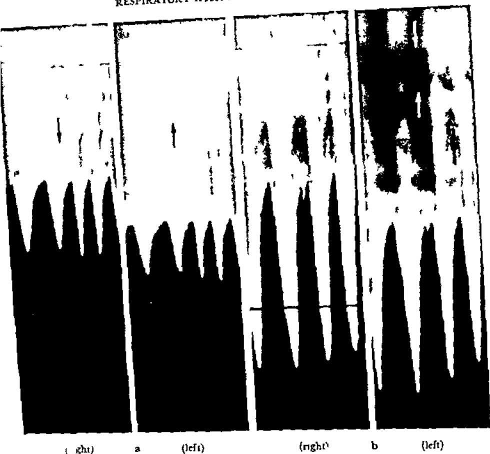


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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF F KNUTSSON),
UNIVERSITY HOSPITAL UPPSALA SWEDEN

TRANSVERSAL TOMOGRAPHY OF THE DESCENDING AORTA

by

HERMAN LODIN

The posterior mediastinum is a region not readily accessible to roentgen investigation The demonstration of the various organs contained in the posterior mediastinum call for the employment of techniques which may include conventional roentgenography of the chest contrast roentgenography of the oesophagus and angiography (for example thoracic aortography) Examination of the oesophagus involves little discomfort to the patient Detailed assessment of the descending aorta however requires the much more complicated and often trying procedure of thoracic aortography Although admittedly it is often possible to establish the position of the left margin of the descending aorta in the conventional film the position of the right border and therefore the width of this structure cannot usually be determined except at its uppermost part Transversal tomography should provide further information about the descending aorta and its width It forms the subject of this communication

In assessing transversal tomograms particular regard must be paid to the errors inherent in the method and dependent upon the morphologic features of the region examined The inherent disadvantages of the method consist mainly in the appearance of blurred outlines of large and dense structures near to the actual layer and in deformation of the image The blurred outlines particularly affect smaller less opaque structures but they are easily re

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SUMMARY

Respiratory kymography was used for studying the diaphragmatic and costal movements in a series of 25 cases of silicosis representing all three stages The use of the method as a qualitative test of respiratory capacity is discussed

ZUSAMMENFASSUNG

Die respiratorische Kymographie wurde in 25 Fallen mit Silikosen aller 3 Stadien benutzt um diaphragmatische und kostale Bewegungen zu studieren Die Anwendung der Methode als qualitativer Test der Respirationskapazitat wird besprochen

RÉSUMÉ

Sur une série de 25 cas de silicose représentant les trois stades, les auteurs ont utilisé la kymographie respiratoire pour étudier les mouvements du diaphragme et des cotes L'utilisation de cette méthode comme test qualitatif de la capacité respiratoire est discutée

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Fig 2 Three variations in the demonstration of the aorta in transversal tomography a) Shallow posterior mediastinum Only the left border of aorta (arrow) is clearly visible Shape and width of aorta not demonstrated b) Deep posterior mediastinum Aorta (arrow) visible in front of the vertebrae The circumference appears oval with the long axis in the frontal plane and is obviously deformed by the heart and vertebral column c) Deep posterior mediastinum Aorta (arrow) in close relation to the left side of the vertebrae is well defined except where in contact with spine Slight deformation

tinum The experiments were carried out with the aid of a Pantix Strator (Zuder Genoa) under the same exposure conditions as in clinical investigations The focus-object distance was about 250 cm and the object film distance about 50 cm the angle of incidence being 25 Ordinary cassettes with double screens and without grid were used

The experiments with the model thorax were intended to elucidate the importance of the heart spine distance as well as the width of the aorta and its position in relation to the heart and vertebral column in the formation of the image in transversal tomography In the experiments therefore the heart spine distance and the thickness and position of the plexiglas aorta were varied The findings may be summarized as follows

1 The greater the heart spine distance the less the deformation and larger will be the part of the circumference of the cylinder (aorta) that will be sharply shown as the distance increases the sector of rotation during which primary tangential rays strike the aorta becomes larger

2 If the aorta is situated in the midline the deformation is less the closer the aorta is to the spine (Fig 1) The possibility of its clear demonstration is chiefly determined by the nearest organ in this case the vertebral column Due to the smaller volume of this structure the sector in which the aorta is struck by tangential rays increases

cognized and can be partly eliminated by a good technique, i e the use of adequately penetrating rays and contrasty films The deformation of the image that sometimes occurs has been analysed by BONTE et coll (1955), OLIVA et coll (1957), and others, who found it to be determined by the mutual relationship of the site, size and absorption density of the object It occurs when the object, during rotation, is struck by the image forming beam only in certain sectors, and is being masked by other, more opaque structures during other phases of rotation

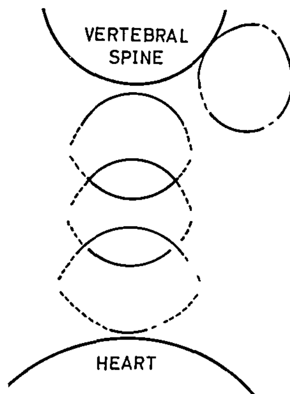


Fig 1 Schematic illustration of the deformation of a cylindrical object (aorta) in the posterior mediastinum The varying degree of deformation depends on the position of the object in relation to other organs such as the heart and vertebral column The ideal position of the aorta is to the left of the vertebral spine Sharp contour ——— unsharp contour — — —

The morphologic features of the region in question are highly significant in this connection From the point of view of transversal tomography the conditions in the posterior mediastinum are particularly difficult, because the structures are bounded posteriorly by the vertebral column and anteriorly by the heart, both of which are dense, the heart in particular is of a considerable size These features impair the visibility of the posterior mediastinal structures, since the demonstration of these structures chiefly depends on the amount of primary tangential (i e contour forming) beam An unfortunate combination of the tomographic disadvantages and anatomical conditions may even lead to failure in demonstrating certain structures if the directly tangential beam is insufficient

The conditions for the use of transversal tomography in the diagnosis of mediastinal hernia were discussed in an earlier paper (LODIN 1957) in connection with model experiments in reproducing linear structures The present investigation is concerned with the representation of cylindrical structures (such as the aorta) in model experiments, the results being compared with the findings in clinical roentgen examinations

Experiments with the model thorax

A model thorax made of 'plexiglas (LODIN 1957) was used Plexiglas cylinders of varying diameter representing the aorta were placed in the posterior medias



Fig 2 Three variations in the demonstration of the aorta in transversal tomography a) Shallow posterior mediastinum Only the left border of aorta (arrow) is clearly visible Shape and width of aorta not demonstrated b) Deep posterior mediastinum Aorta (arrow) visible in front of the vertebrae. Th circumference appears oval with the long axis in the frontal plan and is obviously deformed by the heart and vertebral column c) Deep posterior mediastinum Aorta (arrow) in close relation to the left side of the vertebrae is well defined except where in contact with spine Slight deformation

tinum The experiments were carried out with the aid of a Pantix Strator (Zuder Genoa) under the same exposure conditions as in clinical investigations The focus object distance was about 250 cm and the object film distance about 50 cm the angle of incidence being 25 Ordinary cassettes with double screens and without grid were used

The experiments with the model thorax were intended to elucidate the importance of the heart spine distance as well as the width of the aorta and its position in relation to the heart and vertebral column in the formation of the image in transversal tomography In the experiments therefore the heart spine distance and the thickness and position of the plexiglas aorta were varied The findings may be summarized as follows

1 The greater the heart spine distance the less the deformation and larger will be the part of the circumference of the cylinder (aorta) that will be sharply shown as the distance increases the sector of rotation during which primary tangential rays strike the aorta becomes larger

2 If the aorta is situated in the midline the deformation is less the closer the aorta is to the spine (Fig 1) The possibility of its clear demonstration is chiefly determined by the nearest organ in this case the vertebral column Due to the smaller volume of this structure the sector in which the aorta is struck by tangential rays increases



Fig 3 Transversal tomogram at the level of the hila
The descending aorta is not visible

3 The more lateral the aorta is situated the less will be the deformation (Fig 1) Deformation is least when the aorta lies lateral to the left hand margin of the vertebral column The more lateral the aorta is situated in the mediastinum the less of it will be masked by the vertebral column and heart at the same time Finally, when the aorta is lateral to the vertebrae, it can be masked by either the vertebral column or the heart only during a certain phase of rotation

4 The greater the diameter of the cylinder (aorta) in relation to the heart and vertebral column the better will it be shown If the aorta is narrow in relation to these organs, and at the same time situated in the midline there is a risk that it may not be seen at all, owing to lack of contrast and the predominance of faint outlines of other structures

Clinical features

The position of the descending aorta varies, but as a rule this organ is situated in close relation to the anterior or lateral aspect of the left hand side of the thoracic vertebrae The aorta may lie very much more medial, however, and

may even make no contact with the vertebral column but lie free in the posterior mediastinum Finally, the relation of the descending aorta to the vertebral column may vary at different levels in one and the same patient

In applying the results of the model experiments to clinical roentgenology therefore it must be borne in mind that conditions will vary from case to case and even within the individual chest The experiments do, however show that the demonstration of the aorta is favoured when this organ is situated laterally as it usually is

In principle the clinical and experimental findings tally The demonstration of the aorta was better throughout in the model experiments however probably because of the purer conditions no regard having been paid to the other organs and soft parts in the mediastinum (for example the oesophagus) which may be continuous with the aorta and reduce its contrast The vertebral column in the living subject was also denser than that in the model

As can be seen from Fig 2 demonstration of the aorta is favoured by a deep mediastinum in which the vessel is situated lateral to and contiguous with the thoracic vertebrae In order to obtain a fairly accurate assessment of the size of the aorta two diameters at right angles to each other should if possible be measured The whole circumference of the vessel is seldom shown although some part is usually visible and an impression can generally be gained of more than half of it Cases do occur however in which the aorta cannot be seen at all (Fig 3)

Conclusion

Transversal tomography only exceptionally gives a true impression of the transverse section of the thoracic aorta The chances of demonstrating the size of the vessel are best in subjects in whom the mediastinum is deep for example patients with scoliosis or emphysema Demonstration of the vessel is also favoured if the subject takes a deep breath thus increasing the heart spine distance and accentuating the difference in contrast between the aorta and lung The large dense adjacent organs the heart and vertebral column are responsible for the unfavourable conditions

It is clear from this study that the outlook for improving our knowledge of the descending aorta with the aid of transversal tomography is limited

SUMMARY

The requirements for the demonstration of a cylindrical object in the posterior mediastinum by transversal tomography are examined in experiments using a model thorax of plexiglas The results are correlated to those of clinical investigations It is evident that deformation of the object greatly limits the value of transversal tomography in the examination of the descending aorta



Fig 3 Transversal tomogram at the level of the hila
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FROM THE DEPARTMENT OF SURGERY (DIRECTOR PROF N OBEL) ROYAL VETERINARY COLLEGE, STOCKHOLM SWEDEN

CERVICAL MYELOGRAPHY WITH A WATER SOLUBLE CONTRAST MEDIUM

An experimental study in dogs

by

BERIT FUNKQUIST

Subarachnoid myelography may be performed both with positive contrast media such as iodized oils (Lipiodol®, Pantopaque®) or water soluble contrast media (Abrodil® Kontrast U®) as well as with negative contrast media (air oxygen) The use of the comparatively rapidly resorbed water soluble Abrodil has been confined to the lumbar region this is because of its irritant properties which have been considered to necessitate previous spinal anaesthesia The iodized oils on the contrary have been used for cervical myelography They have however in addition to the late complications (e g subarachnoid granuloma) caused by their slow resorption the drawback of being unevenly distributed and apt to be broken down into droplets (e g LINDGREN 1954) After lumbar injection which may be required when suboccipital puncture is contraindicated the oil is transported only with difficulty to the cervical region (JIROUT 1958)

Air as opposed to the iodized oils is rapidly resorbed, and has no serious irritant effect on the membranes of the spinal cord This contrast medium is therefore generally used for myelography of the cervical region in man (LINDGREN 1939 ODEN 1953, MURTAGH et coll 1955 JAKOBSEN 1956 JIROUT 1958) On the other hand the gaseous contrast media do not permit such a detailed study of the subarachnoid space and the root sheaths of the spinal nerves as does a positive contrast medium particularly one that is water soluble

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ZUSAMMENFASSUNG

Die für die Demonstration eines zylindrischen Objektes im hinteren Mediastinum bei transversaler Tomographie notwendigen Bedingungen sind mit Hilfe eines Thoraxmodells aus Plexiglas experimentell untersucht worden Die Resultate werden mit denen klinischer Untersuchungen verglichen Es ist offenbar, dass die Deformierung des Gegenstandes die bei der transversalen Tomographie auftritt den Wert der Methode für die Untersuchung der Aorta descendens in grossem Ausmasse begrenzt

RÉSUMÉ

Sur un modèle de thorax en plexiglas l'auteur a étudié les conditions permettant de mettre en évidence par tomographie transverse, un objet cylindrique dans le médiastin postérieur Il compare ces résultats avec ceux des examens cliniques et il montre que la déformation de l'objet diminue beaucoup l'intérêt de la tomographie transverse pour l'examen de l'aorte descendante

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cinylcholine iodide (Celocurin®) in doses of about 0 5 mg/kg bodyweight The contrast medium consisted of Kontrast UO 20 with the addition of 1 mg/ml Xylocaine hydrochloride (FUNKQUIST & OBEL 1960) In some experiments methylene blue was added to the contrast solution This made it possible to determine post mortem which parts of the subarachnoid space had been in contact with the solution

With the animal in the right lateral position or prone position and with the hindquarters elevated to about 45 the contrast medium was injected lumbarly in a dose of 0 3 ml/kg body weight Unless otherwise stated the medium was injected during 10 sec In 7 experiments in all the position of the lumbar needle in the subarachnoid space was doubtful in these cases a test injection of 0 5 ml of contrast medium of the aforementioned composition was given 10 to 20 min before the main injection The experimental conditions were varied as regards the suboccipital withdrawal of spinal fluid before the injection of contrast medium position of the animal (lateral or prone) position of the head and neck during and after the injection and duration of elevation of the hindquarters

In some of the experiments in which lumbar injection of contrast medium was preceded by suboccipital spinal tap the spinal fluid flowing from the suboccipital needle after injection of contrast medium was examined for the presence of iodine by the following rough rapid method One drop of spinal fluid was placed every 15 to 30 sec on a cautery wire that had been heated until it was red hot It was then placed underneath and about 1 cm from a filter paper moistened with 1 starch solution Tests were made with a mixture of spinal fluid and contrast medium the concentration of the latter being known It was found that the filter paper consistently assumed a blue colour within a few seconds when the concentration of the medium was 1 % or over

Roentgenograms of the cervical and anterior part of the thoracic region were taken immediately after the injection of contrast medium and as a rule every 30 sec during the first minutes following it In the experiments in which the hindquarters were elevated for some time the roentgenograms were obtained at longer and varying intervals during the later part of this period The majority of the projections were in the lateral plane The direction of the rays was at right angles to the examining table when the animal was in the lateral position and horizontal when it was in the prone position In some cases the lateral films were followed by frontal views after the animal had been rotated 90

When the roentgenologic examination of the cervical spine was completed the forequarters of the animal were elevated to about 25 Films were then obtained of the lumbar spine to rule out epidural injection In certain cases roentgenograms of the cervical spine were also taken after elevation of the forequarters The animal was kept in this position until it showed signs of waking this was generally 20 to 40 min after injection of the contrast medium It was then placed with the trunk in the horizontal position with the neck and head slightly raised by a pillow It was allowed to remain in this position until it made spontaneous attempts to get up

In most experiments the pressure in the femoral artery was recorded by the method of HANSSON & OBEL (1958)

The experimental conditions were varied as follows

A. Lumbar injection of contrast medium without preceding spinal tap head and neck extended during injection

After lumbar puncture of the subarachnoid space the hindquarters of the animal were elevated With the animal in the lateral position the mixture of contrast medium and Xylocaine was then injected through the puncture needle without preceding drainage of spinal fluid

Number of animals and observation period Three Two of these 3 dogs were used about 1 hour later for further experiments during which 1 of them was killed The other 2 dogs were kept under observation for 2 months after the experiment

Duration of elevation of hindquarters About 4 5 min in every experiment

It has been shown that water soluble contrast media may be used for the roentgenologic examination of the thoracic part of the subarachnoid space in the dog (FUNKQUIST & OBEL 1960) In these experiments a contrast medium to which Xylocaine had been added was injected, without previous spinal anaesthesia, into the lumbar region under light anaesthesia and succinylcholine relaxation, with artificial respiration An account is given in the present paper of a study on the possibilities of extending the use of water soluble contrast media to the examination of the cervical part of the subarachnoid space

Three possibilities exist for myelographic depiction of the cervical subarachnoid space with a water soluble contrast medium

1 The medium is injected suboccipitally, with the forequarters of the animal elevated

2 The medium is injected lumbarly, with the forequarters of the animal elevated, in such doses that it is forced up to the desired level of the cervical spine

3 The medium is injected lumbarly, with the hindquarters of the animal elevated, and is allowed to run of its own accord into the cervical subarachnoid space

In preliminary experiments the first alternative was found to involve a great risk of the highly concentrated medium penetrating into the intracranial part of the subarachnoid space and causing disturbances in function of the central nervous system

The second alternative implies that the whole of the spinal subarachnoid space must be filled with contrast medium The safety margin against damage to the spinal cord by contrast medium has, however, proved to be small on injection of such large quantities (FUNKQUIST & OBEL 1961)

In view of the aforegoing considerations, my experiments on cervical myelography with a water soluble contrast medium have been based on the third alternative, i e lumbar subarachnoid injection with the hindquarters of the animal elevated

I Experiments in dogs without spinal cord compression

Most of the dogs were aged 6 months to 1 year, and weighed from 5 to 20 kg Before the experiment, some of them showed signs of an infectious disease (canine distemper or infectious hepatitis) In certain experiments, the same dog was given two injections of contrast medium, either at an interval of about 1 hour (without interruption of anaesthesia), or at an interval of 14 days

Technical details With the dog under Pentothal nitrous oxide anaesthesia the subarachnoid space was punctured lumbarly (FUNKQUIST 1961) and in certain cases suboccipitally as well (BROOK 1936) Anaesthesia and ventilation were then maintained by artificial respiration with a 4 1 mixture of nitrous oxide and oxygen (Pulmomat Dräger) Complete muscle relaxation was induced and maintained throughout anaesthesia by repeated i v injections of suc



Fig 1 Myelogram of cervical region of a dog after lumbar subarachnoid injection of Kontrast U 20 with 1 mg/ml of Xylocaine hydrochloride Dog in lateral position with hindquarters elevated about 45 and head and neck extended during the injection Contrast medium arrested in the anterior thoracic and posterior cervical region

injection of the same quantity of 10 formalin in physiologic saline The dog was left with the forequarters raised for 24 hours it was then decapitated still in the same position through the atlanto-occipital joint After the fluid present in the subarachnoid space had run out the skull was opened and the brain removed and inspected

Results I

Passage of contrast medium to the cervical subarachnoid space

In the 3 dogs in which lumbar injection of contrast medium was made with the hindquarters greatly elevated but without preceding suboccipital spinal tap the contrast medium was arrested in the anterior thoracic or posterior cervical region (Fig 1)

In other experiments the subarachnoid space was emptied of spinal fluid as completely as possible before injection by means of a puncture needle inserted suboccipitally The contrast medium in roentgenologically demonstrable concentration then reached the cranial part of the cervical subarachnoid space very rapidly often immediately after the end of injection

The distribution of the medium in the cervical subarachnoid space was greatly influenced by the position of the neck Thus when the head and neck of the dog were extended during injection the ventral part of the space was generally well filled as far as the posterior margin of C2 and the dorsal part to the posterior margin of C1 (Fig 2) In some dogs the dorsal line of contrast medium was however inconstant over C3 and C4 If on the other hand, the contrast medium was injected into dogs with the head and neck flexed it was arrested ventrally behind C4 whereas a marked accumulation of the medium was observed in the ventral part of the subarachnoid space in the transition be

B *Lumbar injection of contrast medium with preceding suboccipital spinal tap head and neck extended during injection*

After lumbar puncture of the subarachnoid space, the hindquarters of the dog were raised Following suboccipital puncture the spinal fluid was withdrawn as completely as possible i e until the flow ceased or had reached a constant rate of a few drops per minute The sub occipital needle was then removed the head and neck extended, and the contrast medium injected During the injection, 6 dogs were in the lateral position, and 3 in the prone posi tion

Number of animals and observation period Nine (One of them had been used about 1 hour earlier for an experiment according to A) One dog was killed 2 days later owing to deteriora tion of its general condition (? canine distemper) Three of the remaining dogs were kept under observation for 1 to 2 weeks after the experiment and 5 for 1 to 3 months

Duration of elevation of hindquarters 1 5 min in 1 experiment 2 5 to 3 min in 7, and 4 5 min in 1 experiment

C *Lumbar injection of contrast medium after preceding suboccipital spinal tap head and neck flexed durin injection*

Cervical myelography was performed with the technique described under B i e by lumbar puncture after preceding suboccipital spinal tap but the flexed position of the head and neck as well as the position of the suboccipital needle were retained during and after injection The dogs were in the lateral position during the injection In 8 experiments the spinal fluid flowing from the puncture needle was tested for the presence of contrast medium in high concentration (1 % or over) with the rapid chemical method described earlier Roentgenologic examination in the lateral position was generally continued until the spinal fluid gave a positive iodine reaction In 6 experiments the suboccipital needle was withdrawn after a varying interval the hindquarters remaining elevated the head and neck were straightened after which further roentgenograms were obtained

Number of animals and observation period Seven (Two of them were used for 2 identical ex periments at intervals of about 2 weeks) The observation period after the experiment ranged from 4 days to 4 months but was from 7 to 14 days in most experiments

Duration of elevation of hindquarters 1 to 2 min in 5 experiments and 4 to 14 min in 4

D *Variation in rate of injection*

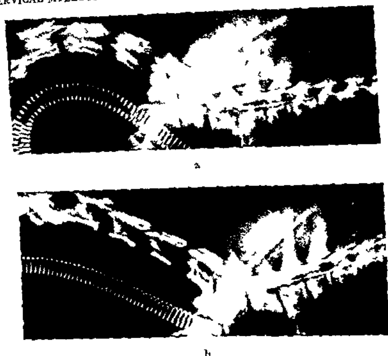
Myelography was performed according to A and B respectively in 3 experiments each but the contrast medium was injected in the course of about 90 sec instead of at the standard rate of about 10 sec The dogs were in the lateral position during injection

Number of animals and observation period Six The observation period after the experiment was 9 days in 1 experiment and 2 to 3 months in 5

Duration of elevation of hindquarters 3 to 4 min

E *Penetration of the contrast medium into the intracranial part of the subarachnoid space*

Myelography was performed according to B and C Methylene blue was added to the con trast medium in such concentration (about 0 5 %) that the tissues with which the solution had been in contact were stained intensely blue During injection the dogs were in the lateral posi tion Each group contained 2 dogs their forequarters were raised for 30 and 60 sec respectively after injection They were killed immediately afterwards by i v injection of Mebumalnatrium 6 % With the dog in the same position the vascular system was perfused with physiologic saline in a dose of about 50 ml/kg bodyweight Fixation was then performed by intra arterial



a

b

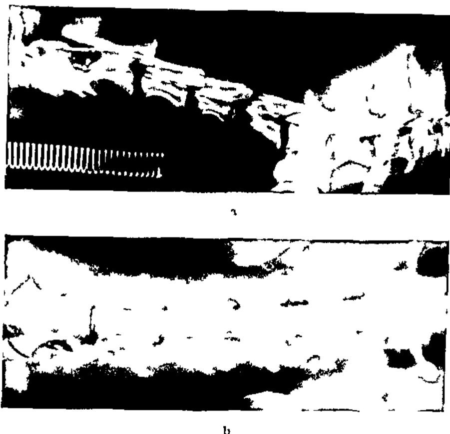
Fig 3 Myelograms of cerv cal region of a dog a) Condit ons as in fig 2a ex cept that the flexed pos tion of the neck for suboccipital pu c tu e was retained dur ng inject on and th puncture needle left in place Marked accumulat on of contrast medium at transit on between cervical and thoracic reg on Dorsally a distinct l n of med um from poste ior margins of C1 to C3 b) Cond tions as n (a) and e posure after extending the neck Med um d splac d in the d ection of the ventral space

The denominator gives the total number of dogs examined roentgenologically at the time in question

Prolongation of the period of elevation of the hindquarters in excess of 60 sec did not result in greater density of the medium except in 1 dog in group B in which the medium reached C2/C3 after 2) min In the other experiments the density remained unchanged or decreased successively in exposures made more than 60 sec after the end of injection

No definite correlation could be demonstrated in the experiments with the neck flexed (group C) between the time of appearance of the iodine reaction in the spinal fluid and the time of optimal density of contrast medium in the cervical subarachnoid space Thus in two experiments the iodine reaction did not appear until after 3 5 and 7 5 min whereas from the roentgenologic point of view a satisfactory amount of medium was already present within 1 min after injection

Comparisons between the quality of the myelograms as regards the ventral



a

b

Fig 2 Myelograms of cervical region of a dog in lateral (a) and dorsal (b) positions Conditions as in fig 1 except that suboccipital spinal tap with the neck flexed was performed immediately before the injection Subarachnoid space filled *ventrally as far as posterior margin of C2 and dorsally to the posterior* margin of C1

tween the cervical and thoracic region (Fig 3a) In this position, the dorsal line of medium was inconstant A distinct dorsal line of contrast medium was, however, generally present from the posterior margin of C1 to that of C2 (Fig 3a) When the head and neck were straightened one or a few minutes after the end of injection, the medium was displaced in the direction of the ventral subarachnoid space (Fig 3b) Its filling was not however, as good as when the medium was injected with primary extension of the neck

In the Table, p 264, is shown the time of appearance of the contrast medium at different points in the cervical subarachnoid space — with sufficient density for diagnostic purposes — in lateral films during myelography according to methods B and C The numerals *0*, *30*, *60* *120* in column *2* denote the time at which the exposure was made, counted in seconds from the end of injection The numerator of the fractions denotes the number of experiments in which contrast medium, at the time in question, was distinctly visible in the subarachnoid space, over the discs specified in the headings of the respective columns

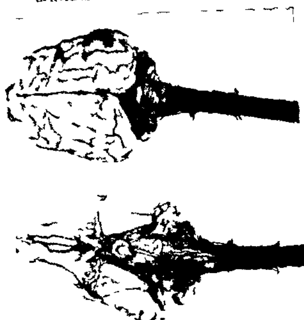


Fig 4 Dorsal and ventral aspects of brain medulla oblongata and spinal cord of a dog after lumbar subarachnoid injection of Kontrast U 20 containing 0 5 methylene blue under conditions described in text Intense blue staining of spinal cord moderate staining of medulla oblongata most of surface of cerebellum and central part of brain stem as far as the optic chiasm

(injection in the lateral position) and 2 in group C One dog in each group was placed with the hindquarters elevated for 30 sec after the end of injection and the other for 60 sec Inspection of the central nervous system after removal of the dura showed in every case intense blue staining of the spinal cord and moderate staining of the medulla oblongata and the greater part of the surface of the cerebellum as well as of the ventral part of the brain stem as far as the optic chiasm (Fig 4) In addition there was faint blue staining ventrally and laterally of the hemisphere that lay lowest in the experiment, the blue colour was particularly distinct along the vessels in the Sylvian fossa No definite difference was present between the two groups with respect to the extent and intensity of staining

Neurologic disturbances

1 *Manifestations localized chiefly to the region of innervation of the cranial nerves* Increased reflex excitability was observed in several experiments on touching the skin of the face during the stage of wakening In addition, 4 dogs had periodic jaw spasms during this stage as well as increased tonus in the neck muscles with a tendency to a flexor position of the neck to the right One dog had increased tonus in the extensor muscles of the front legs as well In 3 of these dogs in which the hindquarters had been elevated for 2 4 5 and 10 min respectively the manifestations lasted 15 45 and 60 min and ceased without

Table

Time of appearance of contrast medium in the subarachnoid space over the anterior intervertebral discs and the atlanto occipital joint respectively

Location of cervical spine on injection of medium and exposure	Interval between injection and exposure sec	Number of animals with contrast filling over the disc in question in relation to number of animals investigated					
		C7—C6	C6—C5	C5—C4	C4—C3	C3—C2	C2—C1
Neck extended (B in text) Dorsally	0	3/4	3/4	2/4	2/4	2/4	3/4
	30	3/4	3/4	2/4	3/4	3/4	1/4
	60	5/6	5/6	4/6	3/6	3/6	3/6
	120	3/4	3/4	2/4	2/4	3/4	2/4
Ventrally	0	1/4	4/4	3/4	2/4	0/4	0/4
	30	1/4	4/4	4/4	3/4	3/4	1/4
	60	6/6	6/6	6/6	5/6	5/6	2/6
	120	4/4	4/4	4/4	4/4	2/4	1/4
Neck flexed (C in text) Dorsally	0	0/6	0/6	1/6	1/6	1/6	1/6
	30	1/3	1/3	2/3	1/3	2/3	1/3
	60	2/5	3/5	3/5	2/5	4/5	2/5
	120	0/1	1/1	1/1	1/1	1/1	0/1
Ventrally	0	5/6	4/6	3/6	0/6	0/6	0/6
	30	3/3	3/3	3/3	1/3	1/3	1/3
	60	5/5	5/5	3/5	1/5	1/5	1/5
	120	1/1	1/1	1/1	0/1	1/1	1/1

subarachnoid space on injection with the dog in the prone and the lateral position, respectively, were made only in group B Of the myelograms of the 3 dogs in which the injection and films were made in the prone position, only one had an amount of contrast medium comparable to that of myelograms with injection in the lateral position

The duration of injection was prolonged to 90 sec (standard time about 10 sec) in 3 dogs in myelography according to A, and in 3 dogs according to B The myelograms showed no definite differences as compared to those obtained with a more rapid rate of injection

After elevation of the forequarters, the contrast medium in the cervical part of the subarachnoid space decreased rapidly in the 6 experiments in group C in which it was checked In roentgenograms taken about 1 min after elevation, the column of medium was extremely diffuse in this region In the lumbar region, on the contrary, the medium was relatively dense at this time

Penetration of contrast medium into the intracranial subarachnoid space

Penetration of the contrast medium into the intracranial part of the subarachnoid space was studied by staining the medium in 2 dogs in group B

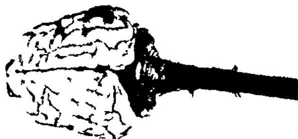




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treatment In the fourth dog (duration of elevation of hindquarters 2 min 45 sec), generalized epileptiform convulsions appeared 15 min after onset of the other signs They were arrested by the i v injection of pentothal in a dose of about 1 cg/kg bodyweight, and did not recur

2 *Spinal manifestations* Of the 25 dogs kept under observation during the first few days after myelography, 4 showed slight to moderate paresis of one hind leg (right leg in 3 cases, left in 1) All 4 dogs had been given further injections of contrast medium, 3 of them as a test injection of 0 5 ml of the medium 10 to 15 min before the main injection, and 1 in the form of two injections (0 5 ml/kg bodyweight) at an interval of about 1 hour None of the other 21 dogs kept under observation exhibited any motor disturbances attributable to the contrast medium, even though 4 of them had received more than one injection in one of the forms described above

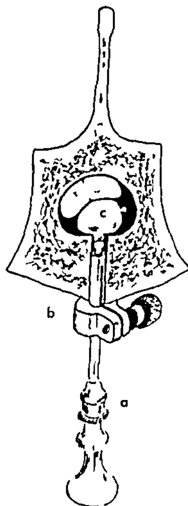


Fig 3 Apparatus for producing controlled compression of the spinal cord

Effect on arterial blood pressure

The effect of the injection of contrast medium on the arterial blood pressure was essentially in agreement with the results of earlier investigations (FUNKQUIST & OBEL 1960) The initial rise lay between 100 and 50 mm Hg in 4 experiments, between 50 and 25 mm in 12, and between 0 and 25 mm Hg in 9 experiments The duration of the rise ranged from 2 to 10 min No marked difference in the rise in blood pressure elicited by injection of contrast medium was present between the groups

Systemic disturbances and mortality

One of the 24 dogs (groups A—D) was killed in direct connexion with the experiment Another dog was killed after a further 2 days because of systemic disturbances (?canine distemper) The remaining 22 dogs survived the experiment, and showed no greater systemic disturbances than those customary after a corresponding duration of anaesthesia alone

II Experiments in dogs with experimentally induced spinal cord compression

Compression of the cervical spinal cord was induced in 4 dogs aged 6 months to 1 year and weighing from 7 to 13 kg This was done by epidural injection of solid paraffin by the following technique

With the dog under pentothal nitrous oxide anaesthesia the ventral surface of the cervical spine was exposed A median hole with a diameter of about 6 mm was bored through the body of one of the cervical vertebrae (C3 C4 or C5) into the vertebral canal A trocar approximately 80 mm long (Fig 5a) with an inner diameter of about 2 mm and an outer diameter of about 3 mm was provided with an outer case (Fig 5b) fitting the bore hole To limit a spread of the paraffin in the epidural space the part of the trocar protruding beyond the outer case was covered by a rubber balloon (Fig 5c) made by double ligation of a valve rubber After application of the rubber balloon the trocar enclosed in its outer case was introduced to such a depth in the bore hole that the outer case was firmly anchored in it The length of the part of the trocar protruding from the outer case was regulated under fluoroscopic control so that the trocar barely reached the internal orifice of the bore hole

Four parts by weight of solid paraffin (m p 69 to 72 C) and one part of Lipiodol were heated and constantly stirred over a water bath to about 100 C and by means of a warmed glass syringe 0 1 ml of the mixture was introduced into the trocar When the mixture had been allowed to cool for about 30 sec it was pressed into the rubber balloon with the mandrin of the trocar This procedure was repeated at intervals of about 1 min between filling the trocar until the dog reacted to introduction of the mandrin by spasms (total quantity 0 1 to 0 8 ml) The trocar was then withdrawn the rubber balloon being pushed off against the edge of the outer case Finally the outer case was also withdrawn from the hole and the muscles and skin were sutured

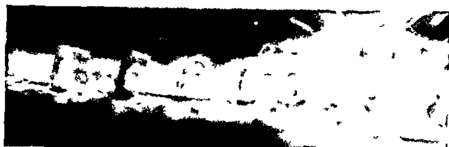
Myelography was performed on all 4 dogs 1 to 3 days after the injection of paraffin It was performed according to technique described under heading I—C, i e with the head and neck of the dog flexed during the first few minutes after injection of contrast medium they were then straightened and further exposures made 3 to 4 min following the end of injection The pressure in the femoral artery was recorded by the method of HANSSON & OBEL (1958) One dog was killed on humanitarian grounds in connexion with myelography Two dogs were kept under observation for 1 day and 3 days respectively after which they were killed In the remaining case laminectomy for the purpose of decompression was performed in direct association with myelography The position and shape of the paraffin plug were studied at autopsy in 3 cases and at operation in 1 case

Results II

The effect of paraffin injection ranged from merely a pain reaction on bending the neck to quadriplegia Optimal filling of the dorsal part of the subarachnoid space as far as the site of compression was obtained as early as within 60 sec Satisfactory filling of the corresponding ventral region did not occur until the neck and head had been straightened In 2 cases traces of contrast medium could also be demonstrated roentgenologically anterior to the site of compression A positive iodine reaction in the spinal fluid flowing from the suboccipital needle appeared in only one case (2 minutes after the end of injection)



a



b

Fig 6 Myelograms of cervical region of a dog with experimentally induced compression of cervical spinal cord a) Epidural injection of solid paraffin with addition of 20 % lipiodol through C5 dog in lateral position b) Compression at C3 dog in dorsal position

The myelographic changes in the form of a filling defect and displacement of the subarachnoid space, respectively, were in good conformity with the position and shape of the compressing paraffin plug (Fig 6) Of the two dogs kept under observation, one (myelography performed 1 day after injection of paraffin) showed slight aggravation of the signs of compression already present before injection of the contrast medium No other signs were observed that could be ascribed to an effect of injection of contrast medium on the central nervous system

The essential changes in blood pressure during and after injection consisted in 3 cases of a rise of 0 to 30 mm Hg with a duration of about 2 min In the remaining case, the pressure rose about 100 mm Hg for 5 min In 1 case a brief fall in pressure to 50 mm Hg occurred when the dog was turned onto its back

III Experiments in dogs with spontaneous spinal cord compression

The series consisted of 9 dogs (7 dachshunds aged 4 5 to 9 years and 2 pekineses aged 1 year and 4 years, respectively) with signs of spinal cord compression in the cervical or anterior thoracic region The clinical features ranged from pain on movement to quadriplegia All of them underwent cervical



Fig 7 Myelogram of cervical region of a dog with clinical signs of compression of cervical spinal cord (prolapsed disc) conditions on myelography as in fig 2a Filling defect of the cervical subarachnoid space over C5 and 4th intervertebral disc (C5, C6) Dorsal displacement of contrast column over the disc (arrow)

myelography, in 7 cases it was performed according to conditions described under heading I—B (head and neck extended during injection) and in 2 cases according to heading I—C (head and neck flexed during injection and for a certain period following it) All the dogs were in the lateral position during injection

Myelography was intended to serve as a basis for therapeutic intervention, and in some cases was carried out before the possible risks of the procedure had been investigated Consequently the period of elevation of the hind quarters and as a result the number of exposures as well was considerably reduced in certain cases The pressure in the femoral artery was recorded by the usual method in 8 dogs

Laminectomy for the purpose of decompression was performed on 3 of the dogs in direct association with myelography The possible detrimental effect of injection of contrast medium could not therefore be established with certainty in view of the operative trauma In 2 cases, the corresponding operation was performed 5 and 7 days respectively after the myelographic examination These 2 dogs and those (4) in which myelography alone was carried out offered a possibility of studying the effects of injection of contrast medium on the existing signs of compression

Results III

Roentgenologic signs of spinal cord compression could be demonstrated in 8 cases whereas in 1 case the myelogram was negative In 7 cases the compression was situated ventrally (over C2—C3 in 1 case C3—C4 in 1 and C5—C6 in 5 cases) (Fig 7) and in 1 case ventrolaterally (over Th2) (Fig 8)

Satisfactory myelograms were obtained in every case even though the last exposure before elevation of the forequarters was already made a few seconds



Fig 8 Myelogram of cervical and anterior thoracic region of a dog with clinical signs of compression of thoracic spinal cord (epidural lipoma) conditions on myelography as in fig 3b Poor filling over Th2 (arrow)

after the end of injection in 1 case, and about 60 sec following it in 5 cases In 2 cases (myelography according to I—B), a sufficient number of films were obtained to judge the time for optimal demonstration of the uncompressed parts of the subarachnoid space (compression at C5—C6) Satisfactory density was present within 30 sec, whereas the myelograms taken after more than 60 sec showed successively decreasing density of the medium

In the 5 cases in which the epidural space was exposed by laminectomy at subsequent operation, the myelographic findings could be completely verified (cervical prolapsed disc in 4 cases and epidural lipoma in 1)

In a few of the 6 cases in which myelography alone was performed primarily, increased reflex excitability on touching the skin of the face was observed when the dog woke from anaesthesia, this sign regressed in a few hours At examination 24 hours after recovery from anaesthesia, slight aggravation of the signs of compression motivating the examination was observed in 3 of the 6 dogs mentioned above The exacerbation subsided within 1 to 2 days in every case As already pointed out, the effect of injection of contrast medium on the central nervous system could not be judged in the 3 dogs operated on in direct association with myelography, in view of the sequelae of operation, one of them (prolapsed cervical disc) was moribund when operation was performed, and died a few days later No clinical manifestations that could be ascribed to injection of contrast medium appeared in the other dogs operated upon once they had recovered from the operative trauma

The arterial blood pressure was largely unchanged in 1 case, moderately raised in 5 cases (rise 30 to 50 mm Hg), and greatly raised in 2 (rise 100 to 120 mm Hg) The rise had a duration of 3 to 7 min A subsequent brief fall in blood pressure occurred in 3 cases,the lowest values being 120, 90 and 65 mm Hg In the first 2 cases, the fall in pressure took place when the dog was turned onto its back or abdomen, respectively, and in the third case in connexion with elevation of the forequarters

Discussion

Two factors seem to be of decisive importance for the passage of contrast medium from the lumbar region into the cervical subarachnoid space They are (1) removal of the spinal fluid from the cervical subarachnoid space before injection of the medium, and (2) the position of the neck during injection

1 Theoretically the contrast medium in view of its greater specific gravity might be expected to run down along the lower margin of the subarachnoid space and reach a sufficient concentration in the cervical region without previous removal of the spinal fluid Experiments with technique I—A have, however shown that such an exchange of fluid does not take place but that the medium is arrested in the posterior part of the cervical region This is probably due to the turbulence arising on contact between the contrast medium flowing in an anterior direction and the spinal fluid collected in the cervical and anterior thoracic regions This dilutes the medium to such a degree that the difference in specific gravity necessary for a rapid exchange of fluid no longer exists

It would obviously simplify matters from the technical point of view if the spinal fluid could be withdrawn through the lumbar needle with the dog s forequarters elevated and thus avoiding suboccipital puncture but preliminary experiments showed that removal of the spinal fluid through a lumbar needle was not definitely effective The probable reason is that the mobile structures present in the lumbar part of the subarachnoid space are apt to block the needle tip when the spinal fluid decreases in volume

2 When as can be inferred from the aforegoing injection of contrast medium must be preceded by suboccipital puncture it might seem reasonable to leave the suboccipital needle in place during the injection It would then be possible — using the method for rapid determination of the presence of contrast medium in the fluid flowing from the needle — to elevate the anterior part of the body as soon as the medium had reached the anterior margin of the cervical region This might diminish the risk of any major quantity of medium passing into the intracranial part of the subarachnoid space On the other hand, if the suboccipital needle were to be kept in place during the injection the head and neck would have to remain in the flexed position used during puncture No correlation seems however to exist between the time at which a positive iodine reaction appears in the spinal fluid and the roentgenologically established time at which the contrast medium reaches the anterior part of the subarachnoid space Moreover the flexed position of the head and neck does not result in satisfactory filling of this portion of the subarachnoid space Consequently in future use of the method there seems to be no reason for leaving the suboccipital needle in situ during the injection

A priori it did not seem to be ruled out that the position of the anterior part of the spine might also affect the possibility of the medium penetrating into the intracranial part of the subarachnoid space The results of the experiments

with stained contrast medium do not, however, indicate that the position of the head and neck is of any great importance in this respect

To sum up, the following statements may be made regarding the role played by the position of the cervical spine during myelography The extended position gives the best depiction of the anterior part of the cervical subarachnoid space, whereas the flexed position promotes filling of the subarachnoid space in the transition between the cervical and anterior thoracic region There is no reason to assume from the results of the experiments that any difference exists between the two alternatives from the point of view of safety

It is remarkable that according to the experiments the risk of any serious damage to the intracranial part of the central nervous system by the contrast medium appeared to be extremely slight This applied even when the animal lay with its forequarters lowered for a relatively long time after the injection It is probable that as a result of the animal's position before the injection the intracranial part of the subarachnoid space and the ventricular system were filled with spinal fluid to such a degree that any medium that might have entered was rapidly diluted Despite this, every endeavour should obviously be made to keep the period of elevation of the hindquarters as short as possible It is therefore essential to bear in mind that passage of the contrast medium from the lumbar to the cervical region seems to take place very rapidly On injection with the neck extended, the medium in 5 of 6 experiments reached the level of C2 30 to 60 sec after injection In the remaining case, the corresponding time was 2 5 min These results should be considered against the background of the fact that spasms of the facial muscles during wakening from anaesthesia have been observed after elevation of the hindquarters for 2 min after injection of the contrast medium There therefore appear to be indications, at least in animals of the size used in these experiments, to standardize the duration of elevation of the hindquarters to 60 sec and, when evaluating the myelogram, to take into account that deficient filling of the subarachnoid space above the level of C2—C3 may occur in normal animals

The only sign of damage to the spinal cord observed in the experimental animals after myelography, was mild or moderate paresis of the muscles of the hind legs with a predilection for the side that was the lower during the injection This occurred in dogs given more than one injection of contrast medium The localization of the damage to the lumbar spinal cord is probably dependent on two factors One is that the concentration of the medium is presumably higher in the lumbar region than in the other parts of the subarachnoid space during and immediately after injection The other is the longer period for which this region is in contact with the medium (test injection confined to the lumbar region, prolonged exposure of the lumbar region to contrast medium in connexion with elevation of the forequarters) If the aforegoing argument is correct, it may be advisable to reinject spinal fluid through the lumbar needle before elevating the forequarters of the animal

A study of the morphologic basis of the functional disturbances will be published separately (FUNKQUIST & OBEL 1961)

The aggravation of the already existing signs of compression that took place after examination is probably to be ascribed to the contrast medium having produced an increase in the volume of the spinal cord It has, in fact been shown in studies to be reported later that lumbar subarachnoid injection of Kontrast U may, under certain conditions cause oedema of the spinal cord (FUNKQUIST & OBEL 1961)

The present results seem to suggest the following procedure in cervical myelography with water soluble contrast media in animals of the size in question After lumbar and suboccipital puncture of the subarachnoid space under i v anaesthesia anaesthesia and ventilation are maintained by artificial respiration with nitrous oxide and oxygen muscle relaxation being produced by administration of succinylcholine iodide The animal is placed in the lateral position, with the hindquarters well elevated After suboccipital withdrawal of the spinal fluid Kontrast U 20 % with the addition of 1 mg/ml of Xylocaine hydrochloride is injected in a dose of about 0 3 ml/kg bodyweight The head and neck of the animal should be kept extended if interest is focused chiefly on examination of the ventral subarachnoid space in the middle and anterior parts of the cervical region If on the other hand examination of the subarachnoid space in the anterior thoracic and the posterior cervical region is required it may be preferable to have the neck flexed Films of the cervical region are obtained during about 60 sec counted from the end of the injection after which the forequarters are elevated so that the contrast medium falls to the thoracic and lumbar regions

SUMMARY

Cervical myelography with a water soluble contrast medium was performed in healthy dogs in dogs with experimentally induced compression of the cervical spine and in dogs with spontaneous spinal cord compression Filling of the cervical subarachnoid space was obtained by the lumbar injection of a mixture of contrast medium and Xylocaine with the hindquarters of the animal elevated following the suboccipital withdrawal of spinal fluid The method did not appear to be associated with any risk of serious circulatory disturbances or persistent damage to the central nervous system

ZUSAMMENFASSUNG

Cervicale Myelographie mit einem wasserloslichen Kontrastmittel wurde bei gesunden Hunden mit experimentell hervorgerufener Kompression des Cervicalmarks und bei Hunden mit spontaner Ruckenmarkkompression durchgefuhrt Ausfullung des cervicalen Subarachnoidalraumes wurde durch lumbale Injektion einer Mischung von Kontrastmittel und Xylocain bei erhohtem Hinterteil des Tieres erreicht wenn die Ruckenmarksflussigkeit durch suboccipitale Punktion vorher entfernt wurde Die Methode scheint mit keinem Risiko fur ernste Zirkulationsstorungen oder Schadigung des Zentralnervensystems verbunden zu sein

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FROM RADIUMHEMMET (DIRECTOR PROF SVEN HULTBERG), KAROLINSKA SJUKHUSET STOCKHOLM, SWEDEN

INCIDENCE OF HYPOTHYROIDISM AND RECURRENCES FOLLOWING I[131] TREATMENT OF HYPERTHYROIDISM

by

ULLA BELING and JERZY EINHORN

Several large series of hyperthyroid patients treated with I[131] have been reported (CHAPMAN & MALOOF 1955 CLARK & RULE 1955 LARSSON 1955, BEIERWALTES & JOHNSON 1956 MCCULLAGH 1956 WERNER et coll 1957 DEGOWIN et coll 1959 LEVINSON 1959 BLOMFIELD et coll 1959 SHELINE & MILLER 1959 ELLER et coll 1960) In the present material the patients were subjected to regular follow up examinations usually at the laboratory where they had received the I[131] treatment The aim of this investigation was to study long term complications notably the incidence of hypothyroidism — as well as recurrences of hyperthyroidism — at varying intervals after treat ment Part of the series the patients treated between 1951 and 1953 has previously been reported (LARSSON)

Material The series consists of patients referred to Radiumhemmet for I[131] treatment of hyperthyroidism More than half of them had been referred from the goiter clinic at the Surgical Department of St Gorans Sjukhus (Dr Hjal mar Wijnbladh) During the period from 1951 through 1956 a total of 854 patients received radioiodine therapy at Radiumhemmet for hyperthyroidism The present series is limited to patients followed up for at least two years and does not include 58 who died within two years after the last I[131] treatment

Submitted for publication 17 April 1961

RÉSUMÉ

L'auteur a fait des myélographies cervicales avec un moyen de contraste hydro-soluble sur des chiens sains, des chiens présentant une compression expérimentalement provoquée de la moelle cervicale et des chiens ayant une compression médullaire spontanée. Après soustraction de liquide céphalo rachidien par ponction atlo occipitale, l'opacification de l'espace sous arachnoidien cervical est obtenue par l'injection d'un mélange de moyen de contraste et de Xylocaine par voie lombaire en surélévant l'arrière train de l'animal. Cette méthode semble n'entrainer ni danger, ni perturbation circulatoire grave, ni lésion du système nerveux central.

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A diagnosis of recurrent hyperthyroidism following I^{131} treatment was recorded when recurrence had been detected one year or more after the last treatment

Statistical methods The cumulative incidence of hypothyroidism m years after the I^{131} treatment was calculated thus

$$r = 1 - q_1 \; q_2 \; q_3 \qquad q_m \tag{1}$$

where $1 - q_1$ is the incidence of hypothyroidism during the first year after I^{131} treatment $1 - q$ is the incidence of hypothyroidism during the second year after I treatment etc

$$1 - q = \frac{a}{n - \frac{d}{2}} \tag{2}$$

where a = the number of patients who became hypothyroid during year i n = the number of followed up euthyroid patients at the beginning of year i d = the number of euthyroid patients followed up for $i - 1$ years but not for i years

$$n \quad = n - a - d \text{ and hence} \tag{3}$$

$$q = \frac{n_+ + \frac{d}{2}}{n - \frac{d}{2}} \tag{4}$$

Since the patients were treated at different periods and some deaths occurred during the follow up period the number fell as the duration of observation increased The results are often reported in the form of curves showing the cumulative incidence of hypothyroidism in relation to the time elapsed since the last I treatment Each point on a curve signifies the incidence of hypothyroidism for at least 50 patients controlled

Results

The incidence of hypothyroidism at follow ups at varying intervals after the I^{131} treatment is shown in Fig 1a One year after the conclusion of radioiodine therapy 7 46 per cent of the patients were hypothyroid During the subsequent observation period approximately 3 per cent of the patients developed hypothyroidism each year This tendency continued throughout the follow up period Seven years after I^{131} treatment the cumulative incidence of hypothyroidism amounted to 26 5 per cent

With the aim of studying the influence of various factors on the incidence of hypothyroidism the patients were grouped with respect to sex type of goiter, age at the time of I^{131} treatment and number of I^{131} therapy doses administered

Factors influencing the incidence of hypothyroidism

The *sex* distribution of hypothyroidism as shown in Fig 1b was even

Table 1

Follow up time in the total series

Years after I^{131} therapy	2—3	3—4	4—5	5—6	6—7	>7
Number of patients followed up	791	672	451	284	165	51

Of the remaining 796 patients, 791 or 99 4 per cent had been followed up for 2 to 8 years Five patients were not available for control

Of the above mentioned 791 patients, 654 were females and 137 males The ages ranged from 19 to 82 and averaged 54 6 years Patients under the age of 40 were treated with I^{131} only on special indications, the series includes 105 such patients The age distribution is shown in Table 3

Methods

The principles of treatment have been previously reported (LARSSON) The method for determination of the initial I^{131} dose was based on estimation of the thyroid weight the 24 hour radioiodine uptake, and the effective half life of I^{131} in the thyroid the aim being to deliver 6 000 to 10 000 rep to the gland In young patients the calculated initial radiation dose was often less than 6 000 rep and in old patients with nodular goiter sometimes greater than 10 000 rep For estimating the weight of the thyroid we usually relied on palpation We sought in some cases to estimate the size of the gland by outlining of the frontal silhouette (HIMANKA & LARSSON 1955) with a heavily collimated directional counter or at a later period by examination with an automatic scintigraph In some patients the effective half life of I^{131} in the thyroid was not estimated and the dose was determined largely with respect to the size of the gland Retreatment doses when indicated were calculated with respect to the effect of the preceding dose Only in a few cases was the radioiodine combined with other specific agents

Radioiodine treatment was repeated at intervals of 2 to 4 months provided the patient remained toxic and the thyroidal I^{131} uptake remained elevated otherwise follow up examinations were made every 2 to 4 months during the first year and subsequently at longer intervals usually 6 months to 1 year Patients were usually examined at Radiumhemmet as well as by the surgeon or physician who had originally referred them for I^{131} treatment In addition to the clinical examination radioiodine tracer tests were repeatedly made Where classification was doubtful the B M R serum cholesterol and P B I were used as criteria

Classed as hypothyroid were all patients requiring permanent thyroid replacement therapy During the first few months after I^{131} treatment transient hypothyroidism may occur The general policy in this series was to avoid thyroid substitution for the first 4 to 5 months after treatment In a few cases however thyroid substitution was for special reasons instituted earlier in order to prevent the development of severe hypothyroidism Where thyroid replacement therapy was instituted one year or more after the radioiodine treatment the clinical picture and laboratory tests had shown unquestionable hypothyroidism No systematic attempts were made to withdraw replacement therapy once it had been initiated (cf WERNER et coll) Some patients discontinued the treatment either of their own accord or in view of the clinical picture on our advice The result in most cases was a return of the clinical hypothyroidism (cf WERNER et coll DEGOWIN et coll RUBENFELD et coll 1959) Those occasional cases in which it was subsequently possible to withdraw replacement therapy were not classed as hypothyroid

For patients who had received several I^{131} treatments the follow up time is counted as from the last treatment (See Table 1)

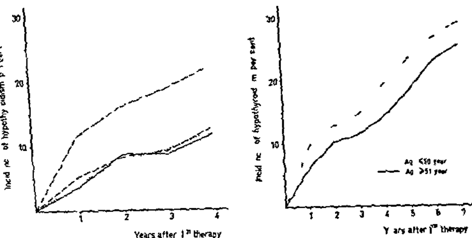


Fig 2 a) Incidence of hypothyroidism following I[131] therapy in 293 hyperthyroid patients without demonstrable goiter (— — —) 218 with toxic diffuse goiter (— — —) 167 with small or moderate toxic nodular goiter ( ) and 108 with large toxic nodular goiter (————) b) Incidence of hypothyroidism in different age groups

SEED & JAFFE (1953), CLARK & RULF, LARSSON, BEIERWALTES & JOHNSON and LEVINSON found in their series a substantially lower incidence of hypothyroidism after I[131] treatment of toxic nodular goiter than after treatment of exophthalmic (both diffuse enlarged and non palpable) goiter Similar observations have been made after surgical treatment of hyperthyroidism (CRILE & McCULLAGH 1951 BARTELS 1953 ERSKIND & CAPPELEN 1955, FOWLER et coll 1956 BEAHRS et coll 1956) In our series, too, a higher incidence of hypothyroidism after I[131] treatment was observed in patients with exophthalmic goiter It was the group of hyperthyroid patients without demonstrable goiter however which were responsible for this The patients with diffuse enlarged toxic goiter in our series showed after long follow up times approximately the same incidence of hypothyroidism as those with nodular goiter In the nodular goiter cases the incidence of hypothyroidism was however somewhat lower one year after the I[131] treatment (Fig 2a) WERNER et coll likewise found a relatively high incidence of late hypothyroidism following I[131] treatment of nodular goiter In their series of 525 patients 40 were hypothyroid within one year after the treatment Only two of those 40 but 7 of the 38 whose hypothyroidism was of later onset, had initially had toxic nodular goiter Several of our patients who became hypothyroid had following the I[131] treatment, substantial residue of the nodular goiter Similar observations have been made after surgical treatment of hyperthyroidism (ERSKIND & CAPPELEN)

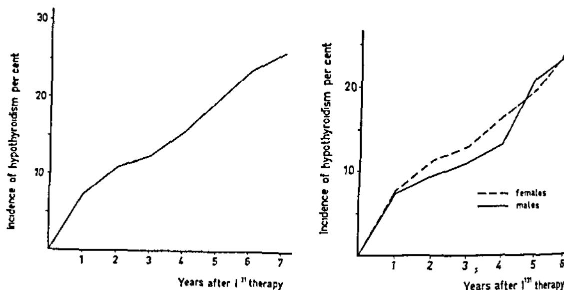


Fig 1 Incidence of hypothyroidism after I^{131} treatment of 791 patients controlled for 2 to 8 years Each incidence is based on the number of patients followed up (Cf Table I) a) Incidence at varying intervals b) Incidence distribution according to sex (654 females and 137 males)

Type of goiter The series was grouped as follows

	Number of patients
Hyperthyroidism without demonstrable goiter (including 78 patients with recurrent hyperthyroidism following thyroidectomy)	298
Diffuse toxic goiter	218
Toxic nodular goiter	
Small or moderate goiter	167
Large nodular goiter	108

The clinical distinction between diffuse and nodular goiter is an arbitrary one (cf MORTENSEN et coll 1955) In this series the diagnosis of nodular goiter was made if one or more discrete nodules were definitely palpable within the gland

As previously reported, the hyperthyroid patients without demonstrable goiter had, after I^{131} treatment, a higher incidence of hypothyroidism than those with palpable thyroid enlargement In our series the respective incidences one year after the treatment were 11 4 and 5 1 per cent Furthermore, the incidence of late hypothyroidism was also greater in patients without demonstrable goiter From the second to the fifth year after I^{131} therapy an additional 15 3 per cent of patients without demonstrable goiter became hypothyroid, compared with only 10 7 per cent of those with palpable thyroid enlargement Patients with diffuse and those with nodular goiter differed only slightly in the incidence of hypothyroidism The difference was likewise small when only the patients with very large nodular goiter and those with diffuse goiter were compared (Fig 2a)

Table 3

Age distribution with respect to incidence of hypothyroidism one year and five years after radioiodine treatment Only 23 patients over 70 had been followed up for 5 years

Age	Number of patients	Hypothyroid % One year after I therapy	Five years after I therapy
<40	105	11.4	24.0
41—50	175	8.6	22.8
51—60	218	7.8	20.0
61—70	213	5.2	13.4
>70	80	5.0	—

that arose in the incidence of hypothyroidism in connection with the treatment remained unchanged at the control examinations Seven years after I^{131} therapy the cumulative incidence of hypothyroidism was 28.8 per cent in patients aged under 50 and 25.3 per cent in those aged over 50 On division into subgroups the age dependence of this incidence was even more conspicuous (Table 3)

The types of goiter in different age groups are shown in Table 4 In older patients hyperthyroidism without palpable goiter was more common than in younger patients In the older patients nodular goiter was found more frequently than diffuse goiter though this cannot account for their lower incidence of hypothyroidism after I^{131} therapy (see Fig 2a)

The older subjects were often treated with somewhat higher doses in order to bring about a relatively swift remission The tendency moreover, was to give smaller I^{131} doses in younger patients in order as far as possible to obviate hypothyroidism This condition was nevertheless more common in the younger subjects The thyroid glands of young patients appear to be more susceptible to I^{131} treatment and thus lower radiation doses should be given

Number of I^{131} treatments per patient The hyperthyroidism was controlled by a single dose of I^{131} in 48 per cent of the patients while 32 per cent required two doses A total of 69 (8.7 per cent) received four or more doses On the average 1.79 therapy doses of I^{131} were administered per patient

The patients cured by one I^{131} dose showed the highest incidence of hypothyroidism (Fig 3a) Worthy of note is the low incidence of early and late hypothyroidism in patients who had received four or more therapy doses

Table 4

Age distribution of goiter types

Age	Hyperthyroidism without demonstrable goiter	Toxic diffuse goiter	Toxic nodular goiter
< 50	34.6	42.9	22.5
> 51	39.1	19.6	41.3

Table 2

Initial I^{131} dose (mC) in different groups of patients In none of the 37 patients with large nodular goiter who were cured by one dose of I^{131} was hypothyroidism observed during the follow up period

	Number of patients	Initial I^{131} dose in the total series		Patients euthyroid after one I^{131} dose		Patients hypothyroid after one I^{131} dose	
		Mean	Range	Mean	Range	Mean	Smallest dose producing hypothyroidism
Hyperthyroidism without demonstrable goiter	298	4 1	1 — 10	4 3	1 5— 8	4 5	2
Toxic diffuse goiter	218	6 2	1 5— 30	6 2	2— 30	6 4	3
Toxic nodular goiter small or moderate	167	7 9	1 5— 30	8 4	2— 30	8 7	3
Large toxic nodular goiter	108	30 8	6 —105	39 0	15—105	—	—

Of the groups investigated, the highest incidence of hypothyroidism was found in the patients with postsurgical recurrence of hyperthyroidism and no demonstrable goiter, the incidence being 16 7 per cent one year after I^{131} treatment and 31 6 per cent five years after the treatment

The incidence of hypothyroidism in each group of patients must depend, at least to some degree, on the dosage of I^{131} administered (See Table 2) However, in other series too, the proportion of patients developing hypothyroidism falls with increasing gland mass (LARSSON, and BLOMFIELD et coll , cf CASSIDY & ASTWOOD 1959) and is highest following I^{131} treatment of postsurgical recurrence (CLARK & RULE, LARSSON) This finding has been attributed to overestimation of the size of non palpable goiters and hence overdosage of I^{131} (LARSSON, BLOMFIELD et coll), and in some at least of the cases that explanation is doubtless correct It is noteworthy, however, that even the incidence of late hypothyroidism has been greater in patients without demonstrable goiter This finding too, is possibly attributable to an I^{131} overdosage which for a time has been compensated It is quite likely however that radioiodine treatment of small thyroid glands will result in a higher incidence of hypothyroidism even after ideal dosage of I^{131}

Age The incidence of hypothyroidism, as previously reported (LARSSON 1955), was higher in the younger than in the older subjects In our series 9 6 per cent of the patients aged under 50, and 6 3 per cent of those past 50, developed hypothyroidism within one year The incidence of late hypothyroidism was the same in young and old patients (Fig 2b) The differences

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the last treatment some measure of selection occurred the patients who required several I^{131} doses were under represented in the groups treated during the first years otherwise the groups treated at different periods were comparable in respect to age and goiter types Of particular interest are the years 1951 through 1954 when all doses were determined by one examiner whose experience of I^{131} therapy increased year by year

Between the years 1951 and 1954 the incidence of hypothyroidism one year after radioiodine treatment fell gradually from 11 3 to 4 0 per cent, subsequently it rose again probably because other less experienced therapists had begun to take part in treatment of the patients (Fig 3b) The declining incidence between 1951 and 1954 was accompanied by some rise in the average number of treatments required This rise was partly attributable to the fact that patients requiring several doses were under represented notably in the group treated during 1951 and 1952 In an earlier survey of the series from 1951—1953 (LARSSON) the year of I^{131} therapy was based on the date of the initial treatment The patients registered for I^{131} therapy in 1951 and 1952 had required on the average about the same number of treatments as those treated in 1953 and the decrease in the incidence of hypothyroidism within one year after treatment was comparable with that reported here

The results of treatment may be expected to improve with the therapist s increasing experience A reduction of hypothyroidism to almost one third of its original incidence is — although coinciding with a certain rise in the duration of treatment — a remarkable improvement which illustrates the importance of experience in dealing with the numerous uncertain factors encountered in I^{131} treatment of hyperthyroidism

Incidence of recurrence of hyperthyroidism after I^{131} treatment

Some patients exhibit after I^{131} treatment a temporary drop in their indices of thyroid function followed within a few months by a return to a level consistent with a clinically lesser degree of hyperthyroidism than that present before the treatment (GORDON et coll 1950 LARSSON CHAPMAN & MALOOF ODDIE et coll 1959) Such cases were not classed as recurrences of hyperthyroidism Recurrence of hyperthyroidism one year or more after the last I^{131} treatment was observed in three of our patients (0 38 per cent), two with nodular and one with diffuse goiter Remission was readily induced by retreatment with I^{131} Recurrences are seldom found after remissions of one year or more following I^{131} therapy the reported incidence in major series varies between zero and 1 1 per cent (Table 5)

None of the patients treated with I^{131} at Radiumhemmet for hyperthyroidism died from or acquired leukemia or thyroid carcinoma The follow up time is too short however for evaluation of the frequency of those complications following radioiodine therapy

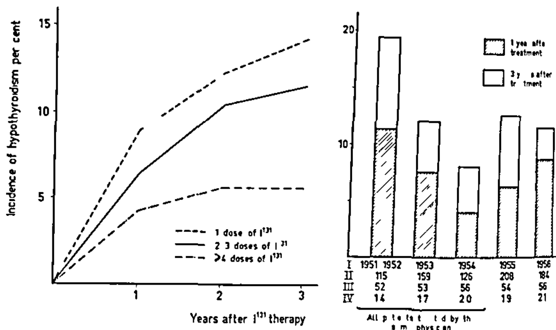


Fig 3 a) Incidence of hypothyroidism in relation to number of I^{131} doses administered b) Incidence of hypothyroidism in relation to year of I^{131} treatment Roman numerals indicate I — year of treatment II — Number of patients III — Mean age IV — Average number of I^{131} doses administered

of I^{131} These patients were few in number, i e 69, though 56 of them were controlled for at least three years

The incidence of hypothyroidism in these different groups depends to some extent on the size of the initial I^{131} dose and the magnitude of the re treatment dosage In other major series too (SEED & JAFFE, SHELINE & MILLER, LEVINSON) hypothyroidism has been more common after a single dose than after multiple doses BALLS et coll (1955) found the reverse in their series

Those of our patients who had received several I^{131} therapy doses showed a lower incidence of hypothyroidism The explanation may be that subjects who are more resistant to radiation treatment and require several doses are less likely than the others to develop hypothyroidism, or it may be that fractionation of the treatment is in some way responsible for the better results

Incidence of hypothyroidism in patients treated during different periods

The incidences of hypothyroidism in patients treated during different periods were compared in order to ascertain the degree to which the results improved with mounting experience This series comprises patients treated during the period 1951—1956 In 1951 and 1952 the patients were relatively few and were therefore combined in a single group consisting of 115 subjects, otherwise the patients were grouped according to the calendar year of I^{131} therapy Since the calendar year was determined arbitrarily by the date of

Hypothyroidism is not regarded as a serious complication, for as a rule it can be readily controlled by substitution therapy When occurring one year or more after the radioiodine therapy however it has a gradual insidious onset and there is a danger that many patients will fail to perceive that something is wrong Frequently there is prolonged mild hypothyroidism which gradually, sometimes over the course of several years (CHAPMAN & MALOOF), develops into complete myxedema ASTWOOD (1960) writes The insidious progression of the myxedema overtakes them so gradually that they lapse into this morbid state without recognizing what is wrong THOREN & WIJNBLADH (1956) in a follow up investigation of surgically treated patients, found that It is not until the follow up that some cases of hypothyreosis were diagnosed These patients had on the whole been satisfied and had considered themselves in good health In view of the high incidence of hypothyroidism after I^{131} therapy patients treated by that method should be followed up indefinitely Where this is impracticable, the patient should be informed about this evidently common complication

If different series of hyperthyroid patients are to be compared in regard to therapeutic results the observation time will have to be taken into account when calculating the incidence of hypothyroidism This incidence will rise with more careful examination and with longer follow up times

Patients may even develop hypothyroidism several years after the surgical treatment of hyperthyroidism A comparison with surgical series with long follow up times (HURXTHAL et coll 1945 BARTELS THOREN & WIJNBLADH, BORGSTROM 1956 IVERSEN et coll 1957) suggests that hypothyroidism is far more common after I^{131} therapy than after surgical treatment Atrophic lesions of cells blood vessels, and stroma that have been observed in the thyroid gland several years after radioiodine treatment (LINDSAY et coll 1954 CURRAN et coll 1958) probably account for the high incidence of late hypo thyroidism following I^{131} therapy No corresponding pathologic changes have been noted after the surgical treatment of hyperthyroidism (CURRAN et coll) The atrophic lesions are probably manifestations of radiation damage, though they could possibly be the result of auto-immunization consequent upon the release of thyroglobulin into the blood stream in connection with the treat ment This hypothesis might be either confirmed or disproved by immunologic studies of patients treated with radioiodine and thereafter followed up over long periods

The question is bound to arise whether the incidence of late hypothyroidism could not be reduced by modification of the therapeutic technique In treat ment with a single I^{131} dose 75 per cent of the radiation dose will be delivered to the thyroid within the course of ten days if the effective half life of radio-iodine in the gland is for example five days It is conceivable that with more protracted irradiation the more radioresistant parts of the gland would be better preserved and subsequent atrophy would be reduced MYANT (1953)

Table 5

Incidence of recurrent hyperthyroidism following I^{131} treatment

Source of data	Number of patients treated	Recurrence of hyperthyroidism number of cases
CHAPMAN & MALOOF 1955	520	1
CLARK & RULE 1955	628	3
MCCULLAGH 1956	1 235	2 (8)
WERNER et coll 1957	525	6
CASSIDY & ASTWOOD 1959	200	0
ELLER et coll 1960	1 308	12
Present series	791	3

Discussion

Hypothyroidism occurring several years after I^{131} treatment has often been reported (SEED & JAFFE, BEIERWALTES 1953, LARSSON, CHAPMAN & MALOOF, WERNER, BLOMFIELD et coll, SHELINE & MILLER, and others)

WERNER et coll in their material of 525 patients, found that 7 6 per cent became hypothyroid during the first year after treatment and an additional 7 2 per cent exhibited myxedema more than one year after treatment The incidence of hypothyroidism more than one year after the treatment was calculated, however, in relation to the total series and not in relation to the number of patients followed up

CASSIDY & ASTWOOD found that of 200 patients with follow up times of 1—7 years, 8 per cent were hypothyroid within one year after I^{131} therapy The incidence of hypothyroidism rose during the ensuing years and, five years after treatment, was reported to be 14 5 per cent It had been calculated, however, not in relation to the number of patients examined at each control but in relation to the total series When the first 101 patients treated in that series were reported (ANDERSSON 1954), 5 8 per cent of those controlled for at least six months were hypothyroid On re evaluation after a longer observation time (CASSIDY & ASTWOOD), the incidence of hypothyroidism had risen to 26 per cent

MACGREGOR (1960) found in his series a 12 per cent incidence of hypothyroidism one year after, and a 17 per cent incidence three years after I^{131} therapy

In the present series 7 46 per cent of the patients developed hypothyroidism within one year after the radioiodine treatment, a figure closely according with the results calculated for other large series The cumulative figure for hypothyroidism seven years after the treatment was 26 5 per cent The curve showed no tendency to level off during the observation period (Fig 1a), and to judge by its course the incidence of hypothyroidism will rise further as the observation time increases

Hypothyroidism is not regarded as a serious complication for as a rule it can be readily controlled by substitution therapy When occurring one year or more after the radioiodine therapy, however it has a gradual insidious onset and there is a danger that many patients will fail to perceive that some thing is wrong Frequently there is prolonged, mild hypothyroidism which gradually, sometimes over the course of several years (CHAPMAN & MALOOF), develops into complete myxedema ASTWOOD (1960) writes The insidious progression of the myxedema overtakes them so gradually that they lapse into this morbid state without recognizing what is wrong THOREN & WIJNBLADH (1956) in a follow up investigation of surgically treated patients, found that It is not until the follow up that some cases of hypothyreosis were diagnosed These patients had on the whole been satisfied and had considered themselves in good health In view of the high incidence of hypothyroidism after I^{131} therapy patients treated by that method should be followed up indefinitely Where this is impracticable the patient should be informed about this evidently common complication

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has discussed such a technique involving small I^{131} doses repeated at intervals of 1 to 2 weeks If the high incidence of late hypothyroidism is due to autoimmunologic reactions, perhaps administration of corticosteroids in conjunction with the radioiodine therapy might reduce the frequency of hypothyroidism

Recurrence of hyperthyroidism following I^{131} therapy is rare the incidence in the present series was 0 38 per cent Hyperthyroidism recurs more commonly following surgical treatment, especially of the less radical kind (HURXTHAL et coll , CRILE & MCCULLAGH) Recurrences may be found many years after subtotal thyroidectomy (CRILE & MCCULLAGH, BARTELS, CHAPMAN & MALOOF, THORÉN & WIJNBLADH), just as hypothyroidism may develop many years after I^{131} therapy

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SUMMARY

The incidences of recurrence and of hypothyroidism were studied in 791 patients at varying intervals after I^{131} treatment of hyperthyroidism Radiotherapy with I^{131} tends to lead to hypothyroidism both early and especially late After a long remission however there is small likelihood of recurrence of hyperthyroidism The influence of sex age type of goiter and number of I^{131} therapy doses administered on the incidence of hypothyroidism was studied

ZUSAMMENFASSUNG

Das Auftreten von Rezidiven und Hypothyreoidismus wurde bei 791 Patienten in verschiedenen Intervallen nach Behandlung von Hyperthyreoidismus mit J^{131} studiert Die Strahlenbehandlung mit J^{131} scheint oft zum Hypothyreoidismus zu führen sowohl kurze Zeit als auch besonders lange Zeit nach der Bestrahlung Nach einer langen Remission ist jedoch die Wahrscheinlichkeit fur das Auftreten eines Rezidives des Hyperthyreoidismus gering Der Einfluss des Geschlechts des Alters des Strumatypus sowie der Anzahl der J^{131} therapiedosen auf das Auftreten des Hypothyreoidismus ist studiert worden

RÉSUMÉ

La fréquence des récidives et de l hypothyroidie a été étudiée sur 791 malades à différents intervalles apres traitement de l hyperthyroidie par l I^{131} Le traitement par l I^{131} a tendance a entrainer une hypothyroidie précoce et surtout tardive Mais après une longue rémission la récidive de l hyperthyroidie est peu probable Les auteurs ont étudié l influence du sexe de l age du type du goitre et du nombre de doses d I^{131} sur la fréquence de l hypothyroidie

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has discussed such a technique involving small I^{131} doses repeated at intervals of 1 to 2 weeks. If the high incidence of late hypothyroidism is due to autoimmunologic reactions, perhaps administration of corticosteroids in conjunction with the radioiodine therapy might reduce the frequency of hypothyroidism.

Recurrence of hyperthyroidism following I^{131} therapy is rare: the incidence in the present series was 0.38 per cent. Hyperthyroidism recurs more commonly following surgical treatment, especially of the less radical kind (HURXTHAL et coll., CRILE & MCCULLAGH). Recurrences may be found many years after subtotal thyroidectomy (CRILE & MCCULLAGH, BARTELS, CHAPMAN & MALOOF, THORÉN & WIJNBLADH), just as hypothyroidism may develop many years after I^{131} therapy.

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SUMMARY

The incidences of recurrence and of hypothyroidism were studied in 791 patients at varying intervals after I^{131} treatment of hyperthyroidism. Radiotherapy with I^{131} tends to lead to hypothyroidism both early and especially late. After a long remission, however, there is small likelihood of recurrence of hyperthyroidism. The influence of sex, age, type of goiter and number of I^{131} therapy doses administered on the incidence of hypothyroidism was studied.

ZUSAMMENFASSUNG

Das Auftreten von Rezidiven und Hypothyreoidismus wurde bei 791 Patienten in verschiedenen Intervallen nach Behandlung von Hyperthyreoidismus mit J^{131} studiert. Die Strahlenbehandlung mit J^{131} scheint oft zum Hypothyreoidismus zu führen, sowohl kurze Zeit als auch besonders lange Zeit nach der Bestrahlung. Nach einer langen Remission ist jedoch die Wahrscheinlichkeit für das Auftreten eines Rezidives des Hyperthyreoidismus gering. Der Einfluss des Geschlechts, des Alters, des Strumatypus sowie der Anzahl der J^{131} therapiedosen auf das Auftreten des Hypothyreoidismus ist studiert worden.

RÉSUMÉ

La fréquence des récidives et de l'hypothyroïdie a été étudiée sur 791 malades à différents intervalles après traitement de l'hyperthyroïdie par l'I^{131}. Le traitement par l'I^{131} a tendance à entraîner une hypothyroïdie précoce et surtout tardive. Mais après une longue rémission la récidive de l'hyperthyroïdie est peu probable. Les auteurs ont étudié l'influence du sexe, de l'âge, du type du goitre et du nombre de doses d'I^{131} sur la fréquence de l'hypothyroïdie.

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FROM MOUNT VERNON HOSPITAL AND THE RADIUM INSTITUTE NORTHWOOD, ENGLAND

RECTAL DOSE AND RECTAL DAMAGE IN THE INTRA CAVITARY TREATMENT OF UTERINE CANCER

by

PAUL STRICKLAND and C GREGORY

It is common clinical experience that the reaction of normal tissues to irradiation is very variable In the most standardised techniques, reactions may vary from mild to severe within a single group of cases, and even if dose discrepancy between that recorded and that actually given is in the region of 10 per cent this is quite insufficient to account for the gross differences observed

We thought it would be interesting to measure and record as accurately as possible the gamma ray dose given to the anterior rectal wall during the course of routine radium or radio active cobalt treatment of cancer of the uterus We hoped to find out from these observations if there was any correlation between the incidence of rectal reactions and the measured rectal dose

For treatment of carcinoma of the cervix a modified Stockholm technique is used This consists of one 50 mg intra uterine tube and two 30 mg ovoids, with modifications of loading if necessary Carcinoma of the body of the uterus is treated by means of an arrangement of Co^{60} sources the method of treatment having been described elsewhere (Jones 1952, STRICKLAND 1953) All cases were treated routinely and no modification was made of treatment time or technique as a result of rectal dose rate measurements

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FROM MOUNT VERNON HOSPITAL AND THE RADIUM INSTITUTE NORTHWOOD ENGLAND

RECTAL DOSE AND RECTAL DAMAGE IN THE INTRA CAVITARY TREATMENT OF UTERINE CANCER

by

PAUL STRICKLAND and C GREGORY

It is common clinical experience that the reaction of normal tissues to irradiation is very variable In the most standardised techniques, reactions may vary from mild to severe within a single group of cases and even if dose discrepancy between that recorded and that actually given is in the region of 10 per cent this is quite insufficient to account for the gross differences observed

We thought it would be interesting to measure and record as accurately as possible the gamma ray dose given to the anterior rectal wall during the course of routine radium, or radio active cobalt treatment of cancer of the uterus We hoped to find out from these observations if there was any correlation between the incidence of rectal reactions and the measured rectal dose

For treatment of carcinoma of the cervix a modified Stockholm technique is used This consists of one 50 mg intra uterine tube and two 30 mg ovoids, with modifications of loading if necessary Carcinoma of the body of the uterus is treated by means of an arrangement of Co^{60} sources the method of treatment having been described elsewhere (JONES 1952 STRICKLAND 1953) All cases were treated routinely and no modification was made of treatment time or technique as a result of rectal dose rate measurements

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Apparatus A scintillation probe and amplifier unit was used for the measurement of rectal dose rate, the basic circuit for the unit having been originally described by GRIFFITH and SWINDELL (1951) In our version of the instrument the scintillation probe consisted of a sodium iodide crystal (thallium activated), a perspex rod and photomultiplier The crystal and perspex rod were contained in a brass tube of an outside diameter of 0 4 cm and length 16 cm, making a light tight attachment to the photomultiplier tube Suitable graduations were marked along the length of the tube The unit has variable E H T, and gain controls making it suitable for a range of dose rate levels, the light output from the crystal appearing on a 0 to 5 μ amperemeter after amplification In order to provide for constancy of performance over a long period, a radium jig was constructed to fit closely round the end of the probe With the jig in position the amplifier gain could be adjusted to give a predetermined reading, thus allowing for variation in sensitivity of the amplifier and photomultiplier units

Calibration A detailed calibration of the instrument and check on performance were necessary before the clinical measurements were started, and subsequent checks on the instrument sensitivity and on the calibration curve were made during its period of use The crystal has directional properties and quality dependence and the importance of these disadvantages were assessed so that appropriate corrections could be made to the clinical measurements

The directional properties of the crystal and light guide were investigated using a discrete source of radium placed at various angles to the probe axis and at varying distances from the crystal Improvements were made to the crystal mounting as a result of these measurements and finally the sensitivity was found to be uniform to within 5 per cent, the response of the crystal being greater for the source placed on the probe axis For extended sources distributed around the probe, in a way such as would be encountered clinically, the variations in sensitivity would not be as large as 5 per cent

The response of the crystal probe to radiations of widely different qualities indicated that the crystal response to radiations of mean energy 80 kV was approximately thirty times the sensitivity found for the gamma rays from radium and Co^{60} The most satisfactory method of obtaining a calibration factor for the probe was to make measurements in a phantom material with an ionization chamber and make a direct comparison of these with measurements made using the probe A water phantom was considered the most convenient, and gynaecological sources consisting of ovoids and tubes were placed in the phantom in a configuration which simulated the ideal treatment conditions The ionization chamber or probe was placed in a fixed position relative to the distributed sources and water added to the phantom to various levels It was found in this experimental set up that the maximum dose rate

reading occurred when the scintillation probe was covered by 4 cm of water and that this maximum reading was 35 per cent greater than a reading obtained without water present From the quality response curve previously obtained such a sensitivity could be expected from a radiation of mean energy 400 kV Finally these measurements were related to measurements obtained in air by using a discrete 70 mg radium source placed at distances along the probe axis This gave a calibration curve which could readily be checked at intervals throughout the period of clinical investigations

It was obvious that a more satisfactory probe unit could be designed which would give a flatter quality response curve, e g anthracene crystal This possibility was investigated when the probe had been in clinical use for some time and although with the anthracene crystal the spectral response was improved, the sensitivity was not as good It was considered better to continue with the existing apparatus rather than alter the instrumentation in the middle of the clinical series The checks and calibrations suggested that the probe readings could be taken as a measure of dose rate in r/hr It must, however be pointed out that the exact disposition of sources with respect to the crystal was not known in the majority of cases and therefore there may have been small changes in sensitivity due to directional and quality effects The apparatus used would we feel give a reasonably good indication of true dose rate in the rectum

Clinical measurements Radium or cobalt insertions were carried out under general anaesthesia in the usual manner, and where radium was inserted into the vagina tight packing was used to increase the distance between ovoids and anterior rectal wall The probe was inserted into the rectum to its full extent with the patient in the lithotomy position Leg clamps were then released and the legs fully extended so that the radium sources should occupy a position approximating to their relationship to the rectum with the patient in bed Moreover, the probe readings were some 10 per cent higher with the patient in lithotomy than in the normal supine position The probe was withdrawn slowly the position of the crystal with respect to the anus being noted from the graduations on the probe and the dose rate recorded Tilting the probe within the lumen of the rectum it was possible to exert slight pressure on the anterior wall The position of maximum dose rate occurred on average 11 to 12 cm from the anus, when ovoids and intra uterine tube were used and at a distance of 12 to 14 cm for Co^{60} sources in the uterus A typical dose rate distribution along the rectum is shown in Fig 1 Measurements were made at each radium or cobalt insertion and the mean of the maximum readings of dose rate were recorded for each particular patient The total treatment time for each patient within a group was the same so that the dose rate information obtained by measurement could be interpreted directly in terms of total dose

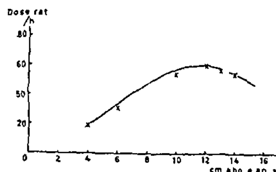


Fig 1 Typical variation of dose rate with distance along the rectal mucosa from a full Stockholm case of 2 × 30 mg ovoids and 1 × 50 mg intra uterine tube Distance measured from the anus in cm

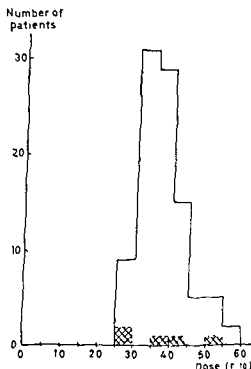


Fig 2 Histogram presentation of the maximum rectal dose measured on 98 cases having 2 × 30 mg ovoids and 1 × 50 mg tube in situ Mean dose rate 55 r/hr ± 13 mean dose 3 620 r ± 860 Incidence of proctitis 5 % of cases

Results and observations

Damage to the rectum in radium treatment of carcinoma of the cervix has been discussed by one of us elsewhere (STRICKLAND 1954) Post radium reaction is defined as a syndrome starting generally within 18 months of treatment and characterised by indefinite rectal pain or discomfort, intermittent diarrhoea, tenesmus and the passage of blood and mucus It is not to be confused with the acute diarrhoea and rectal discomfort which occurs frequently towards the end of any course of radical irradiation where bowel is included within the irradiated volume The mucous membrane in these cases is red and engorged and is sometimes covered by a yellow membrane but the appearances are quite different from those of post radium proctitis Moreover, the symptoms abate rapidly and are not followed by late bowel damage

More often than not post radium damage is self limiting and most cases go on to spontaneous resolution A minority of cases become chronic and after a variable period rectal stricture occurs As this stricture is usually partial obstructive symptoms are uncommon, but occasionally chronic large bowel obstruction may be severe enough to demand colostomy

During the acute phases, the classical appearances of radium proctitis are seen These are described in the standard textbooks on proctology and will not be repeated now In a few cases massive local induration of the anterior wall of the rectum occurs, giving so called 'pseudo carcinoma Even this

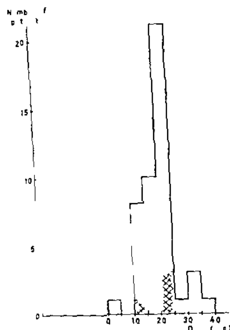


Fig 3 Histogram maximum rectal dose in 45 cases treated for carcinoma of body of uterus using intracavitary Co Mean dose rate 45 r/hr ± 8 Mean dose 2 160 r ± 384 Incidence of proctitis 10 of cases

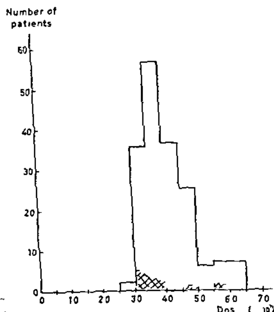


Fig 4 Histogram maximum rectal dose in all cases treated with intracavitary radium or cobalt for carcinoma of cervix and carcinoma of body of uterus Total 169 cases Mean dose 3 500 ± 580 r Dose rate dependent upon treatment technique Incidence of proctitis 2 %

tends to resolve in time but very occasionally fistulous communication may take place between rectum and vagina or rectum and body of uterus or both

In this series specific inquiry was made about any of the symptoms in which we were interested In suspicious cases sigmoidoscopy was performed and the diagnosis confirmed visually No other pathologic cause for the syndrome was encountered in this group but where a history suggestive of rectal reaction was elicited and for a variety of reasons the patient could not be admitted to hospital for clinical confirmation the case was listed as a rectal reaction

By this means we feel confident that the number of reactions recorded is if anything higher than the true number However, a number of our patients died before they had time to develop a reaction so that this probably evens things out in a reasonable clinical way

Group 1 The first group of 98 cases were patients having the modified Stockholm technique two 30 mg vaginal ovoids and one 50 mg intra uterine

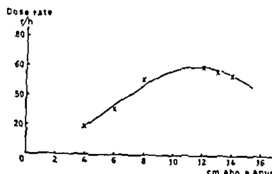


Fig 1 Typical variation of dose rate with distance along the rectal mucosa from a full Stockholm case of 2 × 30 mg ovoids and 1 × 50 mg intra uterine tube *Distance measured from the* anus in cm

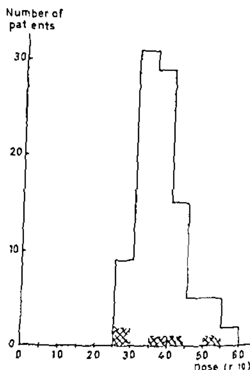


Fig 2 Histogram presentation of the maximum rectal dose *measured* on *98* cases having *2 × 30* mg ovoids and 1 × 50 mg tube in situ Mean dose rate 55 r/hr ± 13 mean dose 3 620 r ± 860 Incidence of proctitis 5 % of cases

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During the acute phases, the classical appearances of 'radium proctitis are seen These are described in the standard textbooks on proctology and will *not* be repeated now In a few cases massive local induration of the anterior wall of the rectum occurs, giving so called 'pseudo carcinoma Even this

ZUSAMMENFASSUNG

Eine Methode zur Messung der Dosisgeschwindigkeit an der Vorderwand des Rektum von Patienten wird beschrieben mit welcher eine intrakavitare Behandlung eines Gebarmutterkarzinomes erhalten wird Eine Scintillationssonde mit einem Natriumjodidkristall mit geeigneter Instrumentierung die eine Direktmessung der Gammastrahlendosisgeschwindigkeit erlaubt wurde benutzt Bei Messungen in 169 Fallen konnte keine positive Korrelation zwischen hoher Strahlendosis und rektaler Reaktion beobachtet werden

RÉSUMÉ

Les auteurs décrivent une méthode de mesure du débit de dose à la paroi antérieure du rectum chez des malades soumises a un traitement intracavitaire pour cancer du col de l utérus Ils ont utilisé une sonde a scintillations à cristal d iodure de sodium avec l instrumentation appropriée permettant la lecture directe du débit de dose gamma Les mesures effectuées sur 169 cas n ont pas mis en évidence de corrélation certaine entre les hautes doses et les réactions rectales

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tube The ovoids have a lead plug at one end which serves to reduce the dose to the rectum if the ovoid is correctly positioned *The radium was left in situ* for a total period of 66 hours, the treatment being carried out in three equal sessions of 22 hours with an interval of seven days between each Measurement of dose rate on the anterior rectal wall and the clinical assessments were made as described The results are presented in Fig 2 Of the 98 cases measured there was a 5 per cent incidence of rectal reaction and the mean dose rate to the rectal wall was 50 to 60 r/hr

Group II These were treated by intracavitary Co^{60} for carcinoma of body of uterus All the sources were within the uterus and the position of maximum dose rate along the anterior rectal wall was further up the rectum than it was in the previous group The mean dose rate lies between 40 to 50 r/hr (Fig 3) and the treatment time was nominally 48 hours, corrections being necessary for Co^{60} decay There is a 10 per cent incidence of rectal reaction — slightly higher than the previous group — the total dose to the rectal wall being somewhat lower than it was in the previous group

Group III There was a small group of cases consisting of patients having partial Stockholm treatment by tube or ovoid only The group was too small to analyse statistically but one important observation was noted, namely that the total dose to the rectum in the modified Stockholm technique can be considered to be one third from the intra uterine tube and two thirds from the ovoids

All cases In Fig 4 the total of 169 cases are presented and the figure clearly shows a negative correlation between high dose and the incidence of rectal reaction

Conclusions Rectal damage would appear to depend on some factor in addition to the dose level to which the rectum is raised during the course of treatment The dose to the rectum was not confined to a small area of mucosa and the shape of the dose distribution along the anterior rectal wall was very similar in all patients investigated, statistically the incidence of rectal reaction in this series is not very high, but the distribution of the series indicates that high dose alone was not the cause of rectal symptoms

SUMMARY

Description of a method of measuring dose rate on the anterior rectal wall of patients undergoing intracavitary treatment for uterine cancer A scintillation probe with a sodium iodide crystal with suitable instrumentation allowing the direct reading of the gamma dose rate is employed No positive correlation between high dose and rectal reaction could be observed in measurements on a material of 169 cases

show an abundant hematopoiesis in the spleen but also an early recovery of the damaged bone marrow Shielding of the bone marrow or other hematopoietic tissues has the same effect as transfusions of autologous bone marrow (JACOBSON 1952)

LORENZ et coll (1951) indicated that in mice a suspension of isologous bone marrow given intravenously or intraperitoneally within 30 minutes of a lethal dose of roentgen irradiation, reduced the mortality from 100 per cent in the control group to 25 per cent in the other two groups In a later study approximately the same amount of bone marrow cells gave a good protective effect in spite of a delayed injection 4 32 or 48 hours following the irradiation (LORENZ et coll 1952) after 72 hours only a limited amount of protection remained and the mortality was as high as 73 per cent It is, however remarkable to find the same number of dead animals when the injection was given 24 hours after the exposure

The sensitivity to ionizing radiation fluctuates in different strains of mice Genetic conditions exist for this according to a paper published from the Research Institute of National Defence (See FROLÉN et coll) The resistance is not only a result of dominant genes but also of additive or recessive genes Treatment with hematopoietic cells at the time of total body irradiation does not give the same result for instance in some strains, good protection was observed after intraperitoneal injection but not in others (LORENZ et coll 1952 CONGDON 1957)

The present investigation was performed in order to find out the optimal time for the marrow injection in our CBA strain which is reported to be resistant to irradiation The intention was also to compare the early as well as the late treatment of bone marrow with Tyrode s solution.

Materials and Methods

Animals Nine hundred and eighty male mice of a CBA strain (imported into Sweden from Dr T C Carter in Harwell) were used in this investigation This strain is inbred by brother-sister mating in 130 generations the last ten being mated in Stockholm The animals were all 9 weeks old when the study started and weighed between 22 and 26 g Commercial cubed food and tap water were available in excess

Radiation factors Th roentgen source was a Muller MG 300 unit operated at 260 kV and 10 mA filter 0.5 mm Cu inherent filtration 4 mm Al dose rate 84 r/min measured with a Moxnes electrometer and a Sievert condenser chamber FOD was approximately 40 cm The animals were irradiated with 1 092 r to the whole body Ten mice were kept in a plastic container divided into ten compartments and irradiated simultaneously In order to obtain uniformity of dosage the plastic wheel was rotated during the exposure at 1 rpm The irradiation was accomplished under mebumal anesthesia (each animal received 0 0015 g intraperitoneally) so as to avoid fracture of the neck during the relatively long (13 minute) exposure After the irradiation the mice were pooled and placed at random in the cages ten to each cage The number of dead animals was counted twice a day during the 30 days

FROM THE DEPARTMENT OF MEDICINE (DIRECTOR G BIORCK), SERAFIMERLASARETTET AND KAROLINSKA INSTITUTET, STOCKHOLM, AND THE MEDICAL DIVISION (DIRECTOR A NELSON) OF THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG, SWEDEN

OPTIMAL TIME FOR MARROW INJECTION IN MICE AFTER TOTAL BODY IRRADIATION

by

BERTIL UNSGAARD

Lethal doses of ionizing radiation in mice produce within a week nearly total depletion of the blood forming tissues Dilatation of sinusoids and cell necrosis including pyknosis and karyolysis of nuclei are among the early changes observed in the bone marrow Pancytopenia is thus produced and is usually complicated by infection and hemorrhages until anemia brings about the death of the animal The protective action of spleen shielding in mice, during exposure to whole body roentgen irradiation or of infusions of hematopoietic cells after irradiation, has been recognized since 1949 (JACOBSEN et coll) In 1951, JACOBSON reported that transplantation of isologous spleens into the peritoneal cavity of mice within half an hour of exposure to 1 025 r total body roentgen irradiation increased the survival rate from 2 3 per cent in the control group to 50 per cent in the experimental group The hematopoietic recovery was complete after 8 days If the implantation was delayed one or two days after the irradiation, only 16 6 per cent survived 28 days The bone marrow was unfortunately not examined in these cases By reason of its hematopoietic capacity the spleen has in mice the ability to take over the function of the damaged bone marrow Spleen shielded mice not only

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Table 1

The 30-day mortality f in the different cages

	K	M 4 hours	M 1 day	M 3 days	M 5 days	M 8 days	T 4 hours	T 1 day	T 3 days	T 5 days	T 8 days
	0 6	0 0	0 2	0 1	0 5	0 6	0 7	0 4	0 6	0 8	0 6
	0 9	0 1	0 1	0 2	0 7	0 3	0 6	0 5	0 6	0 6	0 7
	0 7	0 0	0 0	0 3	0 2	0 8	0 5	0 6	0 6	0 7	0 7
	0 7	0 2	0 0	0 1	0 3	0 5	0 6	0 8	0 4	0 4	0 6
	1 0	0 1	0 1	0.2	0 2	0 6	0 8	0 7	0.8	0 8	0 6
	0 6	0 1	0 1	0 1	0 2	0 2	0 5				
	0 7	0 1	0 0	0.2	0 7	0 5	0 4				
Mean frequency	0 74	0 09	0 07	0 17	0 40	0.50	0 59	0 60	0 60	0 66	0 64

cut off and the medullary canal perfused with Tyrode s solution without heparin During the preparation the container with the suspension was placed in a water bath of 5 C In order to eliminate clumps of bone marrow the suspension was squeezed through a series of No 12 to No 20 gauge needles The marrow (at 37 C) was injected quite fresh or within half an hour after its preparation each animal receiving 0 5 ml of the suspension intraperitoneally The number of living cells injected were estimated at approximately 20×10^6 after standardization of the suspension The counts were made in a haemocytometer on eosin resistant cells The animals were divided into three groups those which received bone marrow (M) those which received pure Tyrode s solution (T) and the control animals (K)

Results

The same amount of isologous bone marrow on an average 20×10^6 nucleated cells was injected intraperitoneally into CBA mice in separate groups five different times after 1 092 r of total body roentgen irradiation The 30-day survival within the different groups is shown in Fig 1 A comparison of the curves indicates that the mortality within the marrow groups increases with the interval of time between the total body irradiation and the treatment while the mortality is unchanged in the groups treated with Tyrode s solution The survival is however identical in the two groups where the bone marrow was given after 4 and 24 hours (91 and 93 per cent) The animals treated with marrow die later than those not so treated except when the injection is given 8 days after the irradiation

The cages were used as units in this investigation *the mortality being observed in every cage* (Table 1) The frequency of mortality of the different cages f has been treated statistically and in order to handle this material more conveniently the frequencies have been transformed according to the wellknown formula $y = 2 \arcsin \sqrt{f}$ (Table 2) At the frequencies 1 and 0 the Bartlett correction has been employed which means that frequency 1 is interpreted as if 1/4 animal had survived and frequency 0 as if 1/4 animal

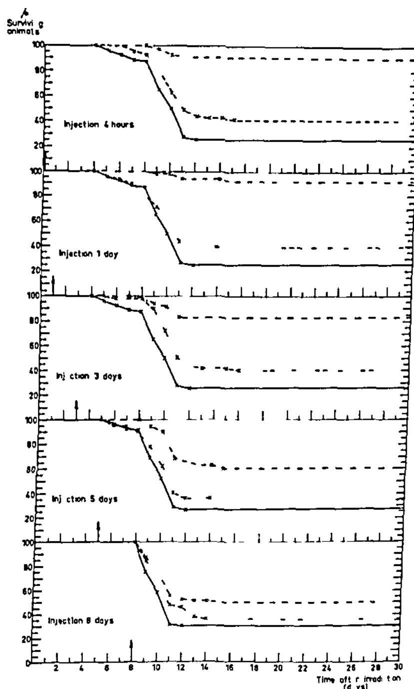


Fig 1 Time survival curves for mice which after total body irradiation received injection in 5 groups at different times of isologous bone marrow (— — —) or Tyrode s solution (— — — —) and for a control group (——) which received no injection

Bone marrow suspension The bone marrow was collected from the femoral bones of twelve to thirteen week old CBA mice of both sexes The bones were cleaned thoroughly from ad hering tissue A needle was inserted in the lower end of each femur the collum femoris was

Table 1

The 30-day mortality f in the different cages

	K	M4 hours	M1 day	M3 days	M5 days	M8 days	T4 hours	T1 day	T3days	T5 days	T8 days
	06	00	02	01	05	06	07	04	06	08	06
	09	01	01	0.2	07	03	06	0.5	06	06	07
	07	00	00	03	0.2	08	0.5	06	06	07	07
	07	02	00	01	03	05	06	08	04	04	06
	10	01	01	02	0.2	06	0.8	07	0.8	08	0.6
	06	01	01	01	0.2	0.2	05				
	07	01	00	02	07	05	04				
Mean fre quency	074	009	007	017	040	050	059	060	060	066	064

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Table 2

The transformed 30 day mortality y, according to the formula $y = 2 \arcsin \sqrt{f}$ *

	K	M_4 hours	M_1 day	M_3 days	M_5 days	M_8 days	T_4 hours	T_1 day	T_3 days	T_5 days	T_8 days
	1.77	0.32	0.93	0.64	1.57	1.77	1.98	1.37	1.77	2.21	1.77
	2.50	0.64	0.64	0.93	1.98	1.16	1.77	1.57	1.77	1.77	1.98
	1.98	0.32	0.32	1.16	0.93	2.21	1.57	1.77	1.77	1.98	1.98
	1.91	0.93	0.32	0.64	1.16	1.57	1.77	2.21	1.37	1.37	1.77
	2.82	0.64	0.64	0.93	0.93	1.77	2.21	1.98	2.21	2.21	1.77
	1.77	0.64	0.64	0.64	0.93	0.93	1.57				
	1.98	0.64	0.32	0.93	1.98	1.57	1.37				
$\bar{y}$	2.11	0.59	0.54	0.84	1.35	1.57	1.75	1.78	1.78	1.91	1.85

* The 95 per cent confidence intervals for $\bar{y}$ are for the first seven columns
(K—T_4) $\bar{y} \pm 0.24$
and for the last four columns
(T_1 day—T_8 day) $\bar{y} \pm 0.29$

Source of variation	Degrees of freedom	Sum of squares	Mean square
Treatments	10	20.3	2.03
Exp. units within treatments	58	6.07	0.105
Total	68	26.37	

$$F = \frac{2.03}{0.105} = 19.3$$

had succumbed (BARTLETT 1947). By means of this transformation a variance independent of the y value is obtained. The expected value of this variance is 1/n (where n is the number of animals in each unit), that is in this case 1/10. The y variable shows a distribution that follows quite close to the normal distribution. The conditions for an analysis of variance are in this way fulfilled.

The variance within the treatments in the analysis was 0.105, that is to say almost exactly the expected value 1/10. The variance between the treatments was 2.03. The quotient of variance, 2.03/0.105 = 19.3, indicates a strongly significant difference between treatments.

It is possible to make some independent comparisons between the different treatments, the most interesting being between early M treatment (M_4 hours + + M_1 day) and early T treatment (T_4 hours + T_1 day), and between late M treatment (M_5 days + M_8 days) and late T treatment (T_5 days + T_8 days). The former is strongly significant and even the latter indicates a clear significance (Fig. 2).

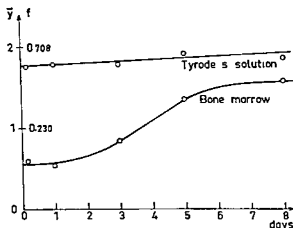


Fig 2 The 30-day mortality f and the transformed 30-day mortality ȳ in relation to treatments with isologous bone marrow or Tyrode s solution at 4 hours 1 day 3 days 5 days and 8 days after irradiation

y treatment 4 hours + 1 day	Late treatment 5 days + 8 days
Mf 0 08	Mf 0 45
Tf 0 59	Tf 0 65

he relation between the 30 day survival in the control group (K) and different groups treated with Tyrode s solution (T), is also significant s is however not valid between the T groups

Discussion

During the whole study the suspension was administered intraperitoneally, ugh injections given intravenously are considered to have a better and a re rapid effect on the blood forming tissues and consequently also on the culating blood (LORENZ et coll 1952) In a pilot test on female CBA mice weeks old the same percentage of survival was found by experiment in the o groups as shown in Fig 3 In this test approximately the same number isologous bone marrow cells 20×10^6 were injected 24 hours after exposure 1 092 r total body irradiation This number of cells may explain the good ult and account for the success of that part of the test where the injections re made intraperitoneally

The given dose of irradiation has been mentioned as approximately an D_{50}/30 days In this material the mortality reached 74 3 per cent in the ntrol group which received no treatment after the irradiation The explana on for this may lie in the fact that the animals were anaesthetized during

Table 2

The transformed 30 day mortality y according to the formula $y = 2 \arcsin \sqrt{f}$ **

	K	M4 hours	M1 day	M3 days	M5 days	M8 days	T4 hours	T1 day	T3 days	T5 days	T8 days
	1.77	0.32	0.93	0.64	1.57	1.77	1.98	1.37	1.77	2.21	1.77
	2.50	0.64	0.64	0.93	1.98	1.16	1.77	1.57	1.77	1.77	1.98
	1.98	0.32	0.32	1.16	0.93	2.21	1.57	1.77	1.77	1.98	1.98
	1.98	0.93	0.32	0.64	1.16	1.57	1.77	2.21	1.37	1.37	1.77
	2.82	0.64	0.64	0.93	0.93	1.77	2.21	1.98	2.21	2.21	1.77
	1.77	0.64	0.64	0.64	0.93	0.93	1.57				
	1.98	0.64	0.32	0.93	1.98	1.57	1.37				
$\bar{y}$	2.11	0.59	0.54	0.84	1.35	1.57	1.75	1.78	1.78	1.91	1.85

* The 95 per cent confidence intervals for $\bar{y}$ are for the first seven columns
(K—T_4) $\bar{y} \pm 0.24$
and for the last four columns
(T_1 day—T_8 days) $\bar{y} \pm 0.29$

Source of variation	Degrees of freedom	Sum of squares	Mean square
Treatments	10	20.3	2.03
Exp. units within treatments	58	6.07	0.105
Total	68	26.37	

$$F = \frac{2.03}{0.105} = 19.3$$

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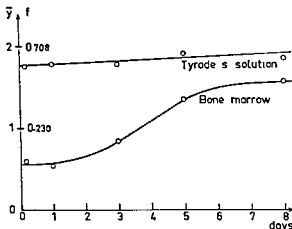


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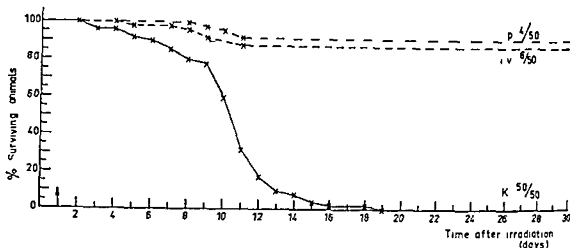


Fig 3 Time survival curves after total body irradiation with subsequent injection of isologous bone marrow intravenously or intraperitoneally (K = control animals)

the exposure through which their metabolism was diminished (LORENZ et coll 1954), and also that they escaped the stress associated with being confined in the container In another experiment going on simultaneously the 30 day mortality was 97 5 per cent in the control group The animals and the conditions for irradiation were exactly the same except that they were conscious during the exposure

The animals died between the 5th and the 16th day, with a maximum of 70 per cent during the 9th to the 11th day Nineteen animals died during the 5th day The corresponding number up to the 8th day inclusive was 67 The majority of these animals died in connection with the injection on the 5th or the 8th day after the irradiation Large subcutaneous hemorrhages were often found in the back of the head and round the site of injection The purpose of this investigation was to prove the effect of a suspension of bone marrow, as compared with pure Tyrode's solution, injected in groups of equal numbers of animals at five different times after the exposure All the animals which died before the treatment, including all which died immediately after the injection, were substituted from reserve cages which had been irradiated at the same time and in the same manner as the original cages of the experiment Twenty reserve animals were assigned to each of the seven days of experiment The animals were taken out at random This procedure explains the fact that the curves start from 100 per cent even when the injection was given 5 or 8 days after the irradiation A selection of animals is thus inevitable for the late treatment This is, however, unimportant, particularly for the reason that a comparison is made between the simultaneous M and T treatments The control animals were favoured as they were never unnecessarily touched in the cages after irradiation

During the first two days after irradiation it is usually impossible to notice any external signs referable to the procedure Several animals acquire during the third day a rough coat From the 5th day all animals are remarkably in active They grow more or less thin and show signs of dehydration Distinct dorsal kyphosis appears The feces are of a cream like consistency and often give a positive benzidine test The signs progress further and reach a maximum between the 9th and the 11th day The mice treated with bone marrow within 24 hours after irradiation are considerably less affected during this period as has been shown before (LOUTIT 1957) Animals not treated with bone marrow and which survive recover more slowly than the marrow treated animals

It seems strange that the mortality in the different groups treated with Tyrode s solution is nearly exactly the same This was considered to be due to the fact that several reserve animals were put in the groups with late treatment A repetition of this part of the experiment was made On this occasion no animals died before the injection The result was the same The effect of Tyrode s solution seems to consist in the supply of fluid

The survival among the irradiated animals bears a direct relationship to the return of the blood forming tissues to a normal state (CRONKITE et coll) The number of bone marrow cells injected decide the survival of lethally irradiated mice doses above 12×10^6 cells give optimal protection (URSO & CONGDON VAN BEKKUM & VOS) The great number of animals in this experiment admit a very accurate statistically guaranteed determination of the effect of bone marrow at the five different times of infection This study which is intended to form a basis for further investigation on CBA mice *confirms* what has previously been found viz that the optimal time of infusion of bone marrow is at 4 hours after irradiation It also shows that the same result is obtained 24 hours after the exposure The marrow cells have, however still a certain effect on the 5th and on the 8th day after the irradiation

Acknowledgements

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SUMMARY

Mice of the CBA strain 9 weeks old were divided in five separate groups and treated with an intraperitoneal infusion of isologous bone marrow at different times after a lethal dose of total body irradiation The results show that the optimal time for the infusion of bone marrow is within 24 hours of the irradiation A certain effect still remains however on the 8th day after the dose

ZUSAMMENFASSUNG

Mäuse des CBA Stammes wurden nach einer Totalbestrahlung mit lethaler Dosis in fünf Gruppen verteilt und mit einer intraperitonealen Einzelinfusion isologen Knochenmarks zu verschiedenen Zeitpunkten behandelt. Die Ergebnisse zeigen, dass der optimale Zeitpunkt für die Infusion des Knochenmarks innerhalb von 24 Stunden nach der Bestrahlung liegt. Ein gewisser Effekt ist jedoch noch am 8. Tage nach der Dosis vorhanden.

RÉSUMÉ

Des souris de la lignée CBA, agées de 9 semaines, ont subi une irradiation de tout le corps à dose léthale; elles ont été réparties en cinq groupes qui ont été traités à des dates différentes après l'irradiation par une injection intrapéritonéale de moelle osseuse isologue. Les résultats montrent que le moment optimum pour l'injection de moelle osseuse se situe dans les 24 heures qui suivent l'irradiation. Le traitement fait le huitième jour après l'irradiation a cependant encore un certain effet.

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FROM THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR M LINDGREN) AND DEPARTMENT OF PATHOLOGY (DIRECTOR C G AHLSTROM) UNIVERSITY HOSPITAL, LUND SWEDEN

DOSE FACTORS AND MORPHOLOGY OF DELAYED RADIATION LESIONS OF THE INTERNAL AND MIDDLE EAR IN RABBITS

by

NILS O BERG and MARTIN LINDGREN

A previous investigation of the effect of roentgen irradiation on the brain in rabbits showed that vestibulo-cerebellar signs were very common (BERG and LINDGREN 1958) This has prompted an analysis of the dose factors and the morphology and site of lesions after roentgen irradiation in single doses as well as fractionated doses to one half of the head of the rabbit This forms the subject of the present communication

Labyrinthine signs not verified histologically The effect of ionizing radiation on the ear was demonstrated as early as in 1905 by EWALD A glass ball containing about 3 mg radium bromide placed in the region of the labyrinth for some hours (the species of animal used was not mentioned) produced after some days signs that were of the same type as those occurring after extirpation of the labyrinth such as turning of the head The severity of the signs varied with the irradiation time

HALBERSTADTER (1920) reported that after mice had been submitted to protracted roentgen irradiation of one side of the skull they ran around in circles with the irradiated side innermost the animals died a few hours later (cit THIELEMANN)

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RUSSEL, WILSON and TANSLEY (1949) described vestibulo cerebellar signs after roentgen irradiation of one half of the rabbit's head from above with 2 850 and 2 440 r (single doses at 200 kV) These were interpreted as manifestations of damage to the CNS

GERSTNER, PICKERING and DUGI (1955) gave a detailed description of the labyrinthine syndrome with turning of the head and 'manege movements' in the rabbit 6 to 100 hours after irradiation with a single dose of 12 000 r to the whole head They stress the similarity of the signs with those referable to destruction of the labyrinth

ABDULLIN (1957) observed delayed effects of roentgen irradiation of the head in pigeons and rabbits with single doses of up to 2 500 r in the form of marked postural disturbances such as opisthotonus, turning of the head to one side, forced rotatory movements, etc (cit LIVANOV and BIRYUKOV 1958)

Labyrinthine signs with morphologic lesions verified histologically MARX (1909) irradiated 15 pigeons with 4 mg radium placed in the right aditus to the tympanic antrum for 30 minutes to 2 hours After a varying interval some of the animals showed typical labyrinthine signs Microscopic examination 2 weeks to 12 months after exposure revealed degenerative and atrophic changes in the sensory epithelium of the vestibule and crista ampullaris The degree of these histologic changes did not vary with the duration of the exposure

MARX also placed 4 mg radium near the apex of the cochlea in the middle ear for 1 hour in 7 guinea pigs Six animals showed no obvious response, while the seventh had typical signs of vestibular damage Histologic examination after 2 5 to 6 months revealed changes in all the animals, similar to those in the pigeons, as well as destruction of the organ of Corti, the spiral ganglion and the cochlear nerve, though the changes were less marked in the animal with no signs He claimed that variation in the position of the radium might have been responsible for the differences in the appearances He was apparently the first to have pointed out the significance of the latency before the appearance of damage by ionizing radiation

CHILOW (1927) placed a glass ampoule containing radium emanation into the tympanic cavity of cats in order to exclude the action of the otoliths Three cats were irradiated, one with a dose of 13 5 mC and the others with 4 mC After 3 days the first animal exhibited marked vestibular signs and died after a week, the other 2 animals showed only slight disturbances of function Any difference in the duration of nystagmus capitis between the two sides was regarded as an effect of irradiation Microscopic examination revealed coagulated lymph in the scala tympani and vestibuli and a varying degree of leukocytic infiltration In the first cat haemorrhages were evident as well as degenerative changes of the sensory cells of the type described by MARX (1909)

THIELEMANN (1929) contributed an important analysis of the radiation damage to the internal and middle ear in mice Soon after roentgen irradiation

the animals presented typical labyrinthine signs and intense hyperaemia, and punctate haemorrhages in the internal ear middle ear and auditory nerve these were followed somewhat later by a serous or seropurulent inflammation of the middle ear and eventual fibrosis

The lowest doses producing changes were a single dose of 8 to 9 HED or a total of 12 8 to 14 6 HED given in two doses at 4 to 5 weeks intervals against the whole head alternating from above and the side The technical data are incomplete but according to the author one HED corresponds to 500 r

Signs did not usually appear until after the second exposure The animals died spontaneously or were killed a few days following the onset of signs The first sign which was observed 24 to 36 hours after irradiation, was hyperacusia Later diarrhoea and loss of bodyweight occurred and the general condition deteriorated Three mice had disturbances of equilibrium with forced rotatory movements the ear reflexes had disappeared in several of the animals

Histologic examination the first few days after irradiation showed intense hyperaemia in the entire region of the ear as well as in the cerebral meninges In animals with signs referable to the internal ear punctuate haemorrhages particularly perilymphatic were present in the vestibule as well as in the auditory nerve middle ear and tympanic membrane No inflammatory reaction was observed at that stage The haemorrhages were often related to the vessels for instance cochlear haemorrhages at the vena canaliculi cochleae although no direct vascular damage was observed It was not until the ninth day that any serous or seropurulent otitis media with oedema and punctate haemorrhages in the mucosa were observed The epithelium was then hed and the exudate became purulent No complications due to sepsis occurred In one animal examined 83 days after being irradiated with 6 8 HED the middle ear had a thickened mucosa with loose fibrosis extending around the auditory ossicles

This brief survey suggests that disturbances of function and morphologic changes may be produced in the labyrinths of experimental animals by radium and roentgen rays Negative results have however also been reported Thus NOVOTNY (1951) found no impairment of hearing or histologic changes in 6 guinea pigs examined 6 weeks after single irradiation with a dose of 1 000 to 7 200 r

The effect of radium irradiation is difficult to judge because the seeds used may produce mechanical lesions In a review published in 1931 DESJARDINS adopted a critical attitude towards these examinations On the other hand the disturbances of function observed by THIELEMANN and others after roentgen irradiation have been confirmed by more recent investigators (RUSSEL et coll, GERSTNER et coll)

Knowledge of the relationship between the doses and morphologic lesions and particularly of the highest dose tolerated without observable damage is thus far from complete

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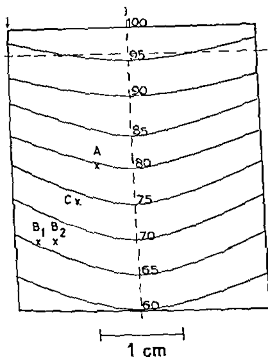


Fig 2a

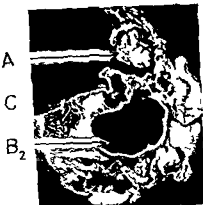


Fig 2b

Fig 2 a) Experimentally determined dose in region of ear (A B and B) in relation to isodose curves in transverse section through centre of field Interrupted line indicates upper surface of brain and arrow midline of brain C = interpolated dose at middle of labyrinth b) Approximate position of measuring points in a section through the ear

and at the lower point about 7 lower The deviation may be explained by the effect of absorption of the radiation in the thick bone around the cerebellum and the inner ear The dose at the centre of the internal ear which lay intermediate between the 2 measuring points and 8 mm from the midline was extrapolated and a value of 68 with a *range of 61 %* to 75 % according to the size of the labyrinth was obtained The depth doses corresponding to the skin doses in the experimental groups are given in Table 4

Results

General and neurologic signs Animals irradiated with higher doses (3 000 to 2 500 r single dose 6 500 r/12 days or 10 500 r/30 days) often showed characteristic signs during the observation period These appeared as a rule between the 15th and 40th week following the end of treatment Many of the animals gradually lost weight their general condition deteriorated and twenty were killed before the end of the observation period The frequency of the various signs in the individual groups is given in Table 1 No signs were observed in two groups (5 400 r/12 days and 6 600 r/30 days)

A clear correlation was found between the size of the dose and the frequency and time of appearance of the neurologic signs in the groups that received large fractionated doses (6 500 r/12 days or 10 500 r/30 days) changes in body weight were only moderate but neurologic signs were often noted

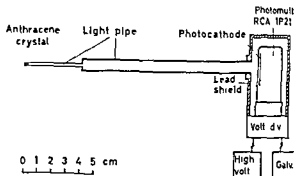


Fig 1 Scintillation dose rate meter for point measurements Sensitive anthracene crystal 1 5 mm long and 1 2 mm in diameter Tube with a highly polished inner wall as light pipe

Material and Methods

Material Seventy nine rabbits were obtained in litters of two to five most of the animals *belonging to litter of 4 animals* Each experimental group was made up of 10 rabbits selected from the different litters in such a way that the mean weight per group was as uniform as possible these mean weights varied between 2 20 and 2 39 kg The animals were observed for 52 weeks following the end of treatment For doses used in different types of treatment see Table 4

Technical data Muller roentgen apparatus MG 300, 200 kV constant potential 10 mA filter 0 5 mm Cu + 1 mm Al half value layer for the quality of the radiation was 0 93 mm Cu dose rate *105 r/min in air FSD 25 cm surface dose 117 r/min*

The roentgen beam was focused over the right half of the skull the left side being shielded with 3 mm lead the hole in the 1 mm mask measured 30 × 40 mm The central ray passed through the centre of the field

Dosimetry The depth doses delivered to the rabbit s brain by this method have been previously described (BERG and LINDGREN 1958) The isodose diagram (Fig 2 a) however holds only for the central parts of the brain these are covered only by the calotte which is *about 1 mm thick and may be neglected as far as radiation absorption* is concerned The internal ear on the other hand is enclosed in a thick layer of bone and is situated about 1 5 cm behind the central parts of the field The depth dose was therefore measured directly

The heads of 2 rabbits (weight 2 3 kg) which had been prepared by the arterial injection of 10 % formalin were used The skulls were sawn horizontally 16 and 25 mm respectively *below the vertex* over the irradiated area Radiation data 175 kV 2 mA 0 5 mm Cu + 1 mm Al giving a half value layer of 0 95 mm Cu FSD 35 cm and field size 30 × 40 cm The measurements were made with a scintillation dosemeter (Fig 1) constructed by LIDÉN and LARSSON (1960)

Three measuring points were selected one in the medulla at a depth of 25 mm and 3 mm from the midline of the skull (B_1) one situated in the floor of the middle ear at the same depth *but 5 mm* from the midline (B_2) and a third point 16 mm below the vertex and 11 mm from the midline in the paraflocculus of the cerebellum (A) i e at the level of the upper semicircular canal (Fig 2b) The dose delivered to each point and the corresponding skin dose were *measured* twice and the values obtained at the individual depths showed good correlation The mean value found for each depth dose was corrected for FSD 25 0 cm

The dose *at a depth* of 16 mm was 77 % and at 25 mm 59 % (the same at 3 and 5 mm from the midline) These values are *compared in Fig 2a with those earlier obtained for the* rabbit s brain It was found that the dose at the upper measuring point was only 2 % lower



a b

Fig 3 a) Twenty five weeks after end of irradiation with 10 500 r/30 The rabbit's head was tilted 90 to the treated side and the animal frequently rolled over on its side nystagmus captus and temporary loss of weight b) From rabbit shown in (a) Fibrosis of middle ear with old hemorrhage at centre Hollow spaces where cholesterol crystals have dissolved Aseptic osteitis in bone walls with lacunar absorption Haematoxylin and eosin × 30

single or a fractionated dose Table 2 gives a survey of the morphologic findings it is clear that the frequency of gross changes decreased with the dose irrespective of the type of treatment The effect of a fractionated treatment of 10 500 r/30 days on the CNS was somewhat less than that produced by 2 500 r but somewhat more than that following a dose of 2 100 r both in single doses Some of the animals in the group that received 6 500 r/12 days had violent vestibulo cerebellar signs with loss of bodyweight after 25 to 30 weeks when the animals were killed The survival of these animals was probably not long enough for any CNS changes to develop A dose of 6 500 r/12 days thus has a greater effect on the CNS than 2 100 r in a single dose

In addition to these frank cerebral lesions discrete changes in the form of small foci corresponding to damage to the small vessels were evident in all the

Table 2

Distribution of marked cerebral lesions in different regions of CNS

Site of lesions	Single dose			Fractionation of dose				
	3 000 r	2 500 r	2 100 r	6 500 r 12 days	5 400 r 12 days	10 500 r 30 days	8 000 r 30 days	6 600 r 30 days
Hemispheres or basal ganglia	8	8	2	1	0	6	0	0
Mesencephalon	3	2	1	1	0	1	0	0
Cerebellum	9	8	0	0	0	2	0	0
Pons or medulla	5	0	0	0	0	0	0	0
Mean survival time in weeks	44	51	51	45	52	50	52	52

Table 1

Frequency of signs in different groups (10 animals in each)

Signs	Single dose 3 000 r	Single dose 2 500 r	Single dose 2 100 r	Fractionation of dose 6 500 r 12 days	Fractionation of dose 10 500 r 30 days	Fractionation of dose 8 800 r 30 days
General						
Loss of bodyweight	7	5	—	3	5	—
Apathy and sopor	1	—	—	2	1	—
Death (unexpected)	—	—	2	—	—	—
Neurologic						
Vestibulo cerebellar	8	4	—	5	8	1
Turning of head temporary	2	1	—	1	1	1
» permanent	6	2	—	3	7	—
Walking in circles	—	—	—	—	1	—
Disturbance of equilibrium	6	2	—	2	5	—
Nystagmus capitis	2	1	—	1	3	—
Rolling over	4	3	—	2	3	—
Miscellaneous						
Irritability	1	3	—	—	1	—
Seizures	—	—	—	3	—	—
Paresis (temporary)	—	—	—	—	—	1
Inequal pupils	—	2	—	—	—	—
Loss of corneal reflex	1	—	—	—	—	—
No signs	1	4	8	5	2	7
Death before 52nd week	7	2	2	3	1	—

Vestibulo cerebellar signs were most common Oblique positioning of the head, which was tilted towards the treated side, appeared in 24 animals The signs were sometimes first detected when the treated animals were gripped by the skin of the back and lifted, later they developed a permanent turning of the head of anything up to 90 degrees (Fig 3a) In some animals this un natural position of the head was transient, but where it was marked the animals usually lay on the right side and stumbled or fell when placed on their feet Some of the animals with disturbances of equilibrium were less affected and could move about in their cages and eat without difficulty

Neurologic signs of the cerebral type were occasionally evident, and mild transient paresis was observed in one animal Three animals had epileptic sei zures, these had co existing vestibulo cerebellar signs Inequality of the pupils and loss of the corneal reflex were noted in a few animals

Histo pathologic findings

The type, extent and distribution of the cerebral lesions have been reported in detail in a previous paper (Berg and Lindgren 1958) The changes in the CNS were mainly of the same histologic type whether the animals received a



Fig 6 10 500 r/30 days Osteogenic sarcoma in bony wall between internal ear and paraflocculus of cerebellum No vestibulo-cerebellar signs H & E × 30



Fig 7 From same rabbit as in fig 5 Involvement of utricle of internal ear H & E. × 83

were not evident Fibrosis in the masticatory muscle was noted in a few rabbits (Fig 4)

Bone changes were most marked around the auditory canal and the middle ear even in the absence of skin necrosis and infection in the 3 000 r and 10 500 r groups The bone showed evidence of lacunar absorption and had been replaced by loose or fairly dense fibrotic tissue (Figs 3a, 4 and 5) Proliferative lesions developing in osteogenic sarcomas were also evident In one of the animals that had received 10 500 r/30 days an osteogenic sarcoma infiltrated the occipital bone and the petrous bone (Fig 6) Most of the animals in the 2 100 r group had only slight lacunar absorption and sclerosis of bone One animal however, had sclerosis of the occipital bone together with a circumscribed area of immature osteoid tissue with cell atypia (? early osteogenic sarcoma) In one animal that had received 2 500 r a tumour with involvement of the internal ear and compression of the medulla pons and cerebellum was evident This tumour which presented histologic features of an osteogenic sarcoma had produced rapidly progressing vestibulo cerebellar signs and a fatal issue

Middle ear Fibrosis and other changes were present in the walls of the middle ear in most of the animals in the 3 000 r and 10 500 r groups In mild cases the mucous membrane was thickened and fibrotic the fibrosis being loose it lined the walls and the ossicles were frequently involved The epithelium was atrophic Very few inflammatory cells were present In two cases the exudate was haemorrhagic (Fig 3b) Purulent inflammation was noted in the more severe cases the epithelium being often completely destroyed the ossicles involved and lacunar absorption evident in the bony walls (Figs 4 and 5),

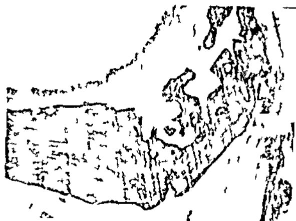


Fig 4



Fig 5

Fig 4 10 500 r/30 days Purulent otitis media with fibrous thickening of mucous membrane and advanced destruction of floor Atrophy with fibrosis in insertion of the masticatory muscle (right lower corner) No lesions in internal ear but facial nerve necrotic Peripheral lesions in nerves and musculature explain turning of the head to irradiated side Van Gieson × 75

Fig 5 10 500 r/30 days Necrosis of wall of middle ear secondary to purulent otitis Van Gieson × 190

groups treated, these lesions were observed in the various groups and their distribution was such as to support the above mentioned conclusions

An analysis of the evaluation of damage to the internal ear and middle ear was made difficult by the high frequency of complications due to infection in some groups The results of the histologic examination of these structures in the animals treated with 2 100 r and 3 000 r in single doses and 10 500 r/30 days doses are described in detail below

Auditory canal, skull bone and soft tissues In the 2 100 r group slight hyperplasia of the epithelium of the canal occasionally occurred In the 3 000 r and 10 500 r groups the auditory canal was often filled with leukocytes and squamous epithelial lamellae, and the epithelium was hyperplastic No cellular atypia was evident In many cases the exudate originated from the middle ear and the ear drum was often perforated or thickened

In a few cases small erosions of the epithelium in the auditory canal and abscesses in the surrounding soft tissues were evident Four animals of the 3 000 r group had diffuse soft tissue changes, which were obviously related to the severe skin reactions with radionecrosis in which abscesses developed these abscesses spread laterally and medially to the base of the skull and into the insertions of the cervical and the masticatory muscles Considerable fibrosis was present around the abscesses together with osteitis which was particularly common in the walls of the auditory canal

In the 10 500 r group the process was more fibrotic and widespread abscesses



Fig 6 10 500 r/30 days Osteogenic sarcoma in bony wall between internal ear and paraflocculus of cerebellum No vestibulo-cerebellar signs H & E. × 30



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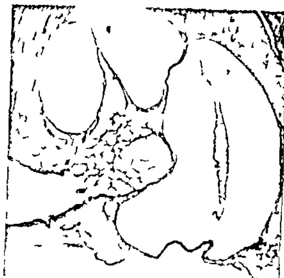


Fig 8 10 500 r/30 days Rarefaction of cochlea and cochlear nerve no evidence of inflammation The rabbit survived the entire experimental period (52 weeks) H & E × 30



Fig 9 From same rabbit as in fig 3 Rarefaction of macula of utricles with complete loss of sensory cells Loss of myelin sheaths in vestibular nerve Van Gieson × 4?

the exudate was often purulent with an admixture of plasma cells and lymphocytes The tensor tympani muscle was fibrotic and atrophic No lesions were detected in the middle ear in the 2 100 r group

Internal ear Like the lesions in the soft tissues and the middle ear those of the internal ear could be divided into an aseptic and an inflammatory group

Acute purulent labyrinthitis was demonstrated in 2 animals in the 3 000 r group with spread of inflammation from the middle ear in both cases In one animal there was an apparently aseptic labyrinthine lesion This animal had widespread soft tissue abscesses which were breaking down into the cerebellum As fibrosis and osteitis were present in the middle ear an inflammatory origin of the lesion of the labyrinth could not be excluded with certainty

One animal in the 10 500 r group had purulent otitis media encroaching upon the internal ear with purulent labyrinthitis (Fig 7) Aseptic lesions occurred in 5 rabbits The membrane of the utricle and saccule and of the semicircular canals was often wrinkled An albuminous exudate with few inflammatory cells and occasional haemorrhage were found in and around the membranous labyrinth In one animal with total necrosis of the auditory nerve rarefaction of the cochlea without inflammatory changes was observed (Fig 8) In 2 animals, the macula of the utricle was completely necrotic and the epithelial cells and the neural elements had been replaced by sparse vacuolized histiocytes (Fig 9) Organisation with histiocytes and fibroblastic cell proliferation was evident and many *histiocytes laden with Fe pigment were present* in the perilymphatic space of the semicircular canals (Fig 10) In one animal,



Fig 10 10 500 r/30 days Destruction of membranous labyrinth with proliferation of loose fibrotic tissue and capillaries Histiocytic cells with Fe pigment in perilymphatic space Commencing new bone formation No sign of sepsis in middle or internal ear The rabbit suffered temporary loss of weight but survived entire experimental period (52 weeks) H & E × 190

commencing new bone formation was visible in one of the semicircular canals (Fig 10) In 3 of the animals with labyrinthine lesions, no evidence of purulent inflammation was found in the middle ear and no histologic signs of a labyrinthine lesion secondary to a previous more active otitis media could be detected The findings indicated in these animals a primary radiation lesion of the internal ear and recent haemorrhages and the abundant iron pigment suggested a primary vascular lesion

No lesions of the labyrinth were apparent in the 2 100 r group

Comparison between the signs and the site of morphologic changes The correlation between the signs and the extent of the lesions in the hemispheres and the basal ganglia was poor Advanced lesions were evident above all in the centrum ovale but had not produced any clinical signs The correlation between the occurrence of vestibulo-cerebellar signs and lesions in the cerebellum, pons and pons nerves and the ears is discussed below

The rabbits with vestibulo cerebellar signs are analysed in Table 3 which also gives the sites of the lesions

In the 3 000 r group the vestibulo cerebellar signs were combined with labyrinthine lesions in 3 animals but all of the animals in this group had cerebellar lesions to a varying extent In 2 rabbits only cerebellar lesions seemed to be responsible for the signs, but the possibility of neural damage cannot be excluded since the nerves were not studied in serial sections

In the 10 500 r group the vestibulo cerebellar signs were associated with morphologic labyrinthine injury in 6 of the animals and in one of them the auditory nerve also was damaged In none of these animals was any cerebellar lesion demonstrable Two rabbits in the 10 500 r group had limited cerebellar lesions in one the head was tilted but the other presented no signs It is thus clear that the vestibulo-cerebellar signs in this group were largely due to peripheral radiation lesions of the labyrinth and/or pons nerves

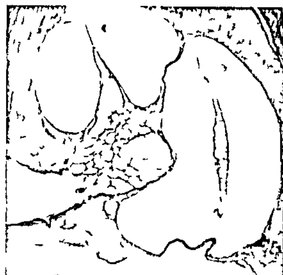


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Table 4

Frequency of vestibulo-cerebellar signs and lesions following various doses (10 animals in each group)

Type of treatment	Single dose (skin) 3 000 r	2 500 r	2 100 r	Fractionation of dose (skin) 6 500 r 12 days	5 400 r 12 days	10 500 30 days	8 800 30 days	6 600 30 days
Vestibulo-cerebellar signs	9	4	0	5	0	8	1	0
Verified lesions in cerebellum pons or nerve roots	9	3	0	1	0	2	0	0
Labyrinthine or auditory nerve lesions								
Verified	5	—	0	—	—	6	—	—
Suggested	—	1	—	4	—	—	1	—
Total	5	1	0	4	0	6	1	0
Labyrinthine dose (± 10 %)	2 000 r	1 600 r	1 400 r	4 400 r	3 000 r	7 100 r	5 400 r	4 500 r

tween the irradiation and the onset of signs was between 4 months and 1 year and the pathogenesis of the lesions varied In some cases the signs could be explained by septic conditions of the middle ear, encroaching upon the internal ear and were occasionally due to osteogenic sarcoma in this region Lesions of the pons and cerebellum were also contributory causes

One group of animals without such complications remains in which the labyrinthine and peripheral neural damage could explain the signs while in another group such an explanation was probable The morphologic analysis revealed labyrinthine necrosis and in several cases a haemorrhagic component or abundant deposition of iron pigment strongly suggested a vascular origin Like THIELEMANN however we were unable to demonstrate any direct vascular lesion

It may be concluded that the pathogenesis of certain late radiation lesions of the internal ear is the same as those in the brain i e the vascular changes seem to be primary especially when the cerebral lesions are discrete (BERG and LINDGREN 1958) At the same time a single haemorrhagic lesion in the labyrinth may cause a transient or permanent labyrinthine syndrome while a corresponding lesion anywhere within a large region of the brain may cause no signs at all

It would appear that the previous sceptical attitude towards disturbances of function due to damage of the internal ear (EWALD 1905 MARX 1909 CHILOW 1927 and others) was not justified Differences in the irradiation technique and the duration of observation period may explain the discrepancies in the histologic appearances reported

Close analysis of the time dose relationship was not possible if only verified pure radiation damage of the internal ear was to be considered Septic lesions

Table 3

Vestibulo cerebellar signs and location of lesions

	Type of treatment	3 000 r (single)	2 100 r (single)	10 500 r/30 days
Signs	Vestibulo cerebellar signs	9 animals	—	8 animals
Site of lesions	Corpora quadrigem	2 animals	1 animal	—
	Cerebellum	All »	—	2 animals
	Pons or roots of pons nerves	5 »	—	—
	Periphery of pons nerves	4 »	—	2 animals
	Labyrinth			
	Aseptic	1 »	—	5 »
	Purulent	2 »	—	1 »
	Middle ear			
	Fibrosis + osteitis	All »	—	7 »
	Ditto + purulent inflammation	3 »	—	4 »
	Teeth			
	Oblique bite	6 »	—	—

A few animals with turning of the head had very small cerebellar lesions and no changes in the pons nerves or labyrinths It is possible that processes in the neck musculature or its insertions might have been responsible for this sign (Fig 4) Oblique wearing down of the teeth was evident in 6 animals of the 3 000 r group and lesions of pons nerves were demonstrated in 4 A lesion of the trigeminal nerve was observed in one animal, this nerve was studied in a few cases only and might have been damaged in more rabbits

Comments Four of the animals in the group that received a single dose of 2 500 r had vestibular signs In 3 of them these could be explained by changes observed in the pons or cerebellum The fourth had probably sustained peripheral neural damage Five of the animals in the 6 500 r/12 days group presented vestibulo cerebellar signs that were often marked Only in one of the animals could histologic changes be detected in the cerebellum to explain the signs and in 4 peripheral damage may be assumed A limited peripheral lesion might have been responsible for transient tilting of the head in one of the animals that received a dosage of 8 000 r/30 days

Discussion

As mentioned in the review of the literature, several investigators have shown that high roentgen doses produce characteristic vestibular signs THIELEMANN stated that these were caused mainly by vascular damage with punctate haemorrhages in the vestibular part of the ear as well as in the eighth nerve

It is evident from the present investigation that marked vestibular lesions and changes in the nerves of the pons occur after a single dose as well as after a fractionated dose and that these produce characteristic signs The interval be

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of the internal ear were fairly common following a single dose but after fractionation of the dose the frequency of such complications was low. A focal dose of 7 100 r/30 days was thus found to produce pure radionecrosis in the internal ear in 50 % of the rabbits.

The septic complications are, however, secondary to mesenchymal radiation reactions of the skin, skull and middle ear. Fibrosis, sclerosis, necrosis and atrophy paved the way for infection. There may therefore be justification for considering lesions of the internal ear irrespective of their pathogenesis.

The frequency of all lesions in the different groups of animals and their relation to the focal doses are given in Table 4 from which is evident that the tolerance doses, i. e. the largest focal doses producing no signs nor morphologic damage to the internal ear, were 1 400 r single dose, 3 000 r/12 days and 4 500 r/30 days. For comparison it might be mentioned that the smallest doses found to produce discrete lesions in the rabbit's brain were 1 300 to 1 700 r single dose, 3 800 r/12 days and 5 000 r/30 days (BERG and LINDGREN 1958). The radiosensitivity of the internal ear and the brain in rabbits thus seems to be of about the same order.

Limited personal experience with high energy radiation suggests the same conclusion. Co^{60} irradiation of one half of the head of rabbits with a single dose of 2 200 r (to the ear) was found to produce no disturbances of function nor morphologic changes in the ear while the smallest dose to produce morphologic cerebral lesions was 2 300 r. These doses correspond to about 1 750 r at 200 kV roentgen (RBE = 0.75, BERG and LINDGREN 1959).

SUMMARY

Vestibulo cerebellar signs and morphologic changes in the ear of the rabbit were observed following roentgen irradiation (200 kV) of half the brain. A single dose of 2 500 r or more complicated the histologic appearances by producing septic lesions in the middle ear and labyrinth. After fractionated irradiation such complications were rare but radionecrosis apparently caused by primary vascular lesions was evident in the labyrinth.

ZUSAMMENFASSUNG

Vestibulo zerebellare Symptome und morphologische Veränderungen traten im Ohr von Kaninchen nach Röntgenbestrahlung (200 kV) der einen Hirnhälfte auf. Bei Einzeitbestrahlung mit 2 500 r oder mehr war das histologische Bild oft durch septische Veränderungen im Mittelohr und im Labyrinth kompliziert. Nach Fraktionierung der Bestrahlung waren derartige Komplikationen selten, man fand jedoch reine Radionekrosen im Labyrinth, welche offenbar durch primäre Gefässchädigung entstanden sind.

RÉSUMÉ

Les auteurs ont observé des symptomes vestibulo cérébelleux et des modifications morphologiques sur l'oreille de lapins ayant subi une irradiation roentgen (200 kV) de la moitié du cerveau. Après une dose unique de 2 500 r ou plus, les aspects histologiques sont compliqués

par des lésions infectieuses de l oreille moyenne et du labyrinthe Après une irradiation fractionnée de telles complications sont rares mais le labyrinthe présente une radionécrose apparemment due a des lésions vasculaires primitives

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BOOK REVIEW

MEDICAL PHYSICS Volume III Edited by Otto Glasser 754 pages, 595 illustrations The Year Book Publishers, Chicago 1960 $ 25

Since the first two volumes of this standard work appeared in 1944 and 1950 the field covered has been rapidly expanding The increasing need which has long been felt for a treatment of recent developments has now been fully met by the third volume

Many articles are new but others are supplementary to articles in the earlier volumes When nothing fresh had to be added only the title of the earlier article and a reference have been entered to take full advantage of the new volume the two earlier volumes should therefore be available No less than four different, alphabetic and systematical indices to the complete series facilitate the finding of any desired information and greatly enhance the usefulness of the new volume

The book is an exclusively North American production, 180 of the 181 authors being residents of the U S A and one of Canada A European reader would hardly class some of the papers e g on anesthesia heart operations hay fever and hypodermic needles as medical physics

An idea of the scope of the work may be conveyed by giving some of the headings of the articles — Application of control system theory in biology Computers (analog and digital) Information theory in biology Radioactive isotopes (several articles) Automatic microscopy Servoanalysis of pupil reflex to light, Space medicine Some of the papers especially the more theoretical ones may be rather difficult for the average reader to understand but a study of the introductory literature which is quoted together with references to the more advanced literature will prove helpful

Among articles of special interest to readers of this journal are those on radiotherapy dosimetry biologic effects of radiation radiation protection radioisotopes autoradiography accelerators roentgen diagnostic methods and image intensifiers It is only in this field that the reviewer can express any opinions on the completeness and correctness of the information given and with few exceptions such as on the article on ionization (p 497—499) they are very favourable It seems a pity that the table of radioisotopes in Volume II (in which the isotopes were grouped according to methods of production) has not now been supplemented with fresh data and the isotopes arranged in the order of atomic numbers instead These are minor criticisms, however and do not detract from the great value of the book

Sten Benner

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ANGIOCARDIOGRAPHIC DETERMINATION OF LEFT VENTRICULAR VOLUME

by

H ARVIDSSON

Determination of total cardiac volume by the conventional technique has long been part of the routine roentgen examinations of the heart at least in Scandinavia ROHRER (1916) was the first investigator to use the sagittal measurements of the heart and not merely its surface in the frontal projection for volume determinations KAHLSTORF (1932 1938) elaborated ROHRER s method and assumed that the heart was shaped as a combined ellipsoid and paraboloid The frontal surface of the heart was determined with the aid of an orthodiagram and the greatest depth was also measured orthodiagraphically According to the ROHRER KAHLSTORF formula the cardiac volume was 0 63 Fa L_m where Fa is the frontal surface and L_m the greatest sagittal measurement Methods based on a three dimensional conception of the heart have also been devised by CIGNOLINI (1928) BOLLINI (1935) and BENEDETTI (1936)

The fact that the geometric magnification need not be taken into consideration with the orthographic technique is an advantage but on the other hand the method is time consuming and exposes the patient to considerable radiation hazards

LILJESTRAND LYSHOLM NYLIN and ZACHRISSON in 1939 published a modification of the ROHRER KAHLSTORF method by which the volume of heart as an ellipsoid was calculated They used teleroentgenography instead of orthodiagraphy and introduced a correction factor for the geometrical magnifica

From Roentgen Department I (Director Docent Gunnar Jonsson) Sodersjukhuset Stockholm Sweden

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tion This method was further modified by JONSELL (1939) who demonstrated that in place of the three theoretical ellipsoid axes three readily identifiable diameters in the heart can with very slight error be employed for measuring the volume With this method the cardiac volume is 0 42 l b d, where l, b and d are the three axes The factor 0 42 is calculated for a film focus distance of 1 5 m, both for frontal and lateral projections, it is only applicable for adult patients with normal body dimensions

With the development of the angiocardiographic technique it has become possible to make intra vitam studies of the volumes of the different heart chambers The right atrium and ventricle are both so irregularly shaped that it is difficult to find any satisfactory method of determining their volume with the use of two orthogonal projections The left atrium and ventricle, on the other hand, are fairly regular in shape and hence lend themselves better to volume analysis Measurement of left atrial volume has been carried out both by cineangiography (GRIBBE et coll 1958, 1959, 1960), and with an ordinary film changer (ARVIDSSON 1958, SOLOFF et coll 1956, 1957)

Two different methods have primarily been employed for measurement of the volume from two projections at right angles, namely (1) planimetric determination of the surface in one or two projections and (2) a determination assuming that the body to be examined has a definite geometric shape and hence using for the measurement certain fixed diameters from which the volume can be calculated With both these methods several assumptions and approximations must be made As was shown earlier (ARVIDSSON 1958), not even with a geometrically defined ellipsoid can the volume be determined with the aid of two orthogonal projections if the orientation of the axes is not known An advantage of the planimetric method of volume measurement is that it permits a volume determination even in the case of a fairly irregular body, but on the other hand the outer contours of the body, whose volume is to be determined, must be wholly defined in the two projections used, a feature seldom occurring at angiocardiography With a volume determination based on three diagonal measurements and assuming the body to be a regular ellipsoid, there is no necessity for the outer contour to be distinguishable in its entirety, the only points that need be identified are those determining the axes of the body The latter method of measuring volume can be fairly easily carried out and thus is suitable for routine work

As regards the choice between cineangiography and an examination with an ordinary film changer, the cine method certainly has the advantage of allowing a high exposure rate, the films obtained however are often of such poor quality, at least in adult patients, that determinations are not easy to carry out A film changer produces good quality views and the measurements can be carried out directly on the films without the necessity of enlargement The relatively low exposure rate is, of course, a disadvantage when rapidly changing volumes and haemodynamic occurrences are to be studied

As the present writer has previously demonstrated it is possible to obtain an approximate value for the volume of the left atrium in man, especially when the chamber is dilated as in mitral disease When dilated, the atrium assumes the shape of an ellipsoid and hence its volume may be measured from the three principal axes of this ellipsoid While a knowledge of the volume and volume variations in the left atrium is valuable in helping us to understand the haemodynamics of the left side of the heart it is even more important to be able to calculate volume variations in the left ventricle Measurement of left ventricular volume is however much more difficult to carry out than a left atrial determination CHAPMAN BAKER REYNOLDS and BONTE (1958) made left ventricular volume studies in the dog and in man with the aid of biplane cine fluorography They started by using Simpson s parabolic formula for determination of the volume of irregular bodies As this method is very time consuming they subsequently changed over to an empirical formula based on experiences from volume measurement by Simpson s method The empirical method they used was based on a planimetric determination of the ventricular area in two projections at right angles If the product of the two surface projections of the ventricle is X and the volume is Y then $\log Y = -0.4444 + 0.8216 \log X$

GRIBBE, HIRVONEN, LIND and WEGELIUS (1959) also applied cineangiography for determination of left ventricular volume in the dog Using planimetric measurement as well as measurement of the axis lengths in the ventricle they found very little difference between the two methods and thus chose the latter technique for their subsequent volume studies These authors also corrected for papillary muscles and trabeculae carneae by determining the volume of these tissues at autopsy and then subtracting this intracavitary muscular volume from the estimated ventricular volume GRIBBE (1960) later made a comparison between a minute volume determination by the Fick method and by angiocardiography in dogs and cats and obtained good agreement between the two methods

Equipment and Methods

A GIDLUND (1956) biplane film changer allowing exposure of 6 pairs of films per second was used at all examinations with a 6-valve Elema Triplex Automatic 1 000 CE apparatus with a maximum voltage of 140 kV as generator The contrast medium employed throughout was Urografin (Schering) 60 containing 290 mg of iodine per ml and it was injected with a GIDLUND injection syringe In order to localize the exposures in the heart cycle ECG tracings with simultaneous recording of exposures and injection were made with an Elema four-channel Mingograph as the electrocardiographic apparatus The minute volume was calculated with an oxygen breathing spirograph manufactured by AB Instrumenta Lund Sweden

Projections True antero-posterior and lateral projections were used at all examinations partly because these are suitable for left ventricular measurement and partly because exactly the same projections may be readily reproduced in the event of a renewed examination possibly postoperatively at a later date

tion This method was further modified by JONSELL (1939) who demonstrated that in place of the three theoretical ellipsoid axes three readily identifiable diameters in the heart can with very slight error be employed for measuring the volume With this method the cardiac volume is 0 42 l b d, where l, b and d are the three axes The factor 0 42 is calculated for a film focus distance of 1 5 m, both for frontal and lateral projections, it is only applicable for adult patients with normal body dimensions

With the development of the angiocardiographic technique it has become possible to make intra vitam studies of the volumes of the different heart chambers The right atrium and ventricle are both so irregularly shaped that it is difficult to find any satisfactory method of determining their volume with the use of two orthogonal projections The left atrium and ventricle, on the other hand, are fairly regular in shape and hence lend themselves better to volume analysis Measurement of left atrial volume has been carried out both by cineangiography (GRIBBE et coll 1958, 1959, 1960), and with an ordinary film changer (ARVIDSSON 1958, SOLOFF et coll 1956, 1957)

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pressure a series of films were taken with 6 exposures per second during contrast filling of the left side of the heart This final exposure phase lasts about 5 seconds For injection into the pulmonary artery 1 3 to 2 ml of contrast medium per kg of bodyweight and an injection rate of 20 to 40 ml per second were used

This method has proved valuable for the study of the left atrium, mitral orifice left ventricle, and aorta (ARVIDSSON) In cases with considerable dilatation of the left heart the concentration of contrast medium in the left ventricle is sometimes so low that the outlines of this chamber are difficult to distinguish in the films The method has two advantages, first that it is relatively risk free, and secondly that disturbances in the heart rhythm seldom occur during the roentgenographic phase in which the left ventricle is visible this is a valuable factor for the construction of volume curves (see a later section)

2 *Contrast medium injection into left ventricle* In several cases the contrast medium was injected directly into the left ventricle after retrograde arterial catheterization from the right radial artery This method as well as its range of application has been described by HANSSON JONSSON and KARNELL (1959) This examination also is begun with right heart catheterization, a pressure recording, and a minute volume determination by Fick s method The right radial artery is then exposed and a No 9 or 10 side hole catheter is inserted into the aorta where a pressure recording is made The catheter is then passed through the aortic orifice into the left ventricle and the pressure is recorded again Pressures are then recorded while the catheter is withdrawn to demonstrate if there is a systolic gradient over the aortic orifice in other words whether there are signs of aortic stenosis In order to confirm any clinical suggestion of aortic insufficiency a small amount of contrast medium (30 to 40 ml Urografin 60 %) is injected into the ascending aorta in these cases During the injection 6 to 9 pairs of film are exposed at a rate of 3 exposures per second This part of the examination is carried out without general anaesthesia Immediately after this aortography the catheter is again passed down into the left ventricle and general anaesthesia is produced in the same way as already described under points (A) to (E) in connection with the pulmonary artery injection With the left ventricle injection method the intrapulmonary pressure is kept at a fairly high level (about 20 mm Hg) from the beginning An amount of 0 8 to 1 ml Urografin 60 % per kg of bodyweight is injected at a rate of 25 to 30 ml per second During and after the injection, 6 pairs of films per second are exposed in antero posterior and lateral projections over a period of about 4 seconds This technique gives a complete angiocardiographic picture of mitral and aortic disease and it has been found that the left ventricle can be reached even in cases with relatively severe aortic stenosis

The method has two drawbacks In the first place, with the method we have used it is necessary to sacrifice a radial artery In all probability, however,

Exposure data The examinations were made on adult patients and the exposure data were as follows

	kV	mA	sec
A p projection	90 to 120	300	0 01
Lateral projection	90 to 120	200 to 300	0 01

As both tubes were driven by the same generator kilovoltage and exposure time were the same in both projections Variations in density in different patients were compensated for by altering the tube voltage

Determination of minute volume by the Fick method The oxygen consumption was recorded with a spirograph while the patient was breathing 100 per cent O_2 and at the same time the arterio venous oxygen difference was measured in samples taken simultaneously from the pulmonary and brachial arteries The oxygen saturation in the samples was determined by the van Slyke technique In a few cases duplicate determinations were carried out and these showed that the method possesses good reproducibility This minute volume determination was made 15 to 30 minutes before the angiocardiography The heart rate was measured during the determination so that the stroke volume could be ascertained in cases with regular sinus rhythm

Roentgenographic demonstration of the left ventricle

In the main, two different methods were used for demonstrating the left ventricle

1 *Contrast medium injection into the pulmonary artery* After the usual catheterization of the right heart, with pressure recording, blood gas analysis, and minute volume determination by the Fick method, a No 9 or 10 USCI catheter with side holes was manoeuvered so that its tip lay in the main pulmonary artery General anaesthesia was then achieved in accordance with the following scheme

A 35 to 50 mg meperidine, intravenously
B 100 to 150 mg sodium pentothal, intravenously
C About 50 mg succinylcholine iodine, intravenously
D Endotracheal intubation with a cuff tube
E Maximum oxygenation of the patient
F Injection of the contrast medium while the anaesthetist kept the intra pulmonary pressure at a low level (0 to 5 mm Hg), while the medium was being injected 6 to 9 pairs of films were exposed in order to allow a study of the pulmonary blood vessels
G When the medium was estimated to have passed through the lungs the intrabronchial pressure was slowly raised to about 20 mm Hg by oxygen inflation

The time usually required for the contrast medium to pass through the lungs is between 3 and 6 seconds, depending on the cardiac volume and the pressure in the pulmonary circulation, the greater the cardiac volume and the higher the PA and PCV pressures the slower is the passage of the medium through the lesser circulation In conjunction with the raising of the intrapulmonary

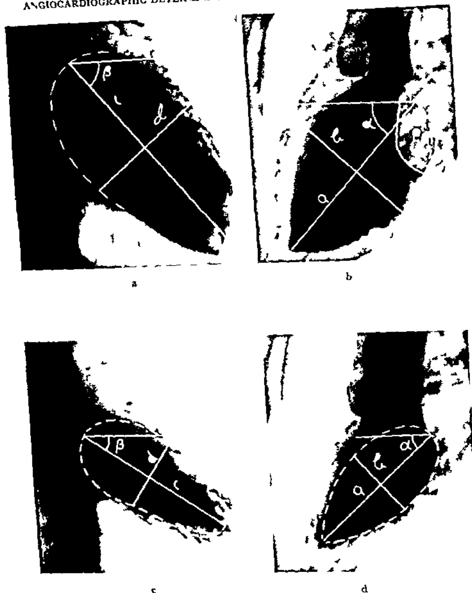


Fig. 1. Method of left ventricular volume determination. Left ventricular contrast medium injection in a case of mitral stenosis and aortic incompetence. (Case not included in this material.) a) A-p projection at end of diastole. Top of ventricular ellipsoid completed. Pouch formed by ballooning mitral leaflet can be traced in left upper part of left ventricle. Axes of ellipsoid are drawn. b) Lateral projection in same heart phase as (a). Pouch formed by mitral leaflets (P) clearly defined. Papillary muscles partially visible. c) A-p projection at end of systole. Top of ellipsoid is not easy to identify. d) Lateral projection in same phase as (c). Top of left ventricular ellipsoid is formed mainly by the anterior mitral leaflet. Papillary muscles included in the volume determination.

it should be possible to catheterize the left ventricle after percutaneous puncture of the femoral artery, at least in cases with no aortic stenosis. In the second place, when contrast medium is injected into the left ventricle extrasystoles often occur during the actual injection. The heart usually returns to its normal rhythm after only a few abnormal beats, however. A whole series of extrasystoles sometimes occur during the examination and prevent satisfactory measurement of the left ventricular volume and, in isolated cases, sinus tachycardia may reduce the possibilities for volume determinations.

Material

The purpose of the present work was to study the possibility of making angiocardiographic left ventricular volume determinations with clinically satisfactory accuracy. Selected cases were therefore taken from among the extensive angiocardiographic material in the department. The material consists for the most part of acquired lesions not involving demonstrable incompetence in either the mitral or aortic orifice, nor were there signs of shunt in any of the cases. As the angiocardiographic technique has shown itself to be relatively risk free the indications for the examination have gradually been widened, and the material contains patients with sound hearts with only a vague suggestion of cardiac disease. As already mentioned, a number of cases were rejected, for the following reasons:

1. A minute volume determination by the Fick method had not been performed, or had been unsuccessful. As this form of minute volume determination came into use as a routine measure in the department in 1958 all older cases consequently had to be rejected.
2. Fibrillation or other severe disturbance of rhythm had been present during the examination, this prevented determination of the stroke volume. A few cases with regular fibrillation rhythm were included.
3. Unsatisfactory electrocardiographic and exposure recording during the examination prevented determination of the position of the films in the heart cycle.
4. Because of unsatisfactory roentgenographic demonstration of the left ventricle adequate volume measurement was not possible.
5. The exposures occurred at such unsuitable positions in the heart cycle that none of the views showed maximum systole and diastole.

The material was thus reduced to 16 cases. In 9 cases the contrast medium was injected into the pulmonary artery and in 7 cases directly into the left ventricle after retrograde catheterization. It may be pointed out that a satisfactory angiocardiographic diagnosis was also obtained in the rejected cases, even though they could not be used for the special purpose of measuring the left ventricular volume variations.

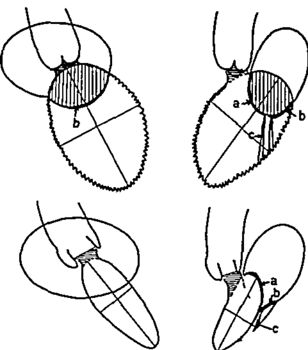


Fig 3 Schematic illustration of details to be considered in the determination of the left ventricular volume especially in mitral stenosis

Top left and right A p and lateral projections in diastole Anterior mitral leaflet (a) posterior leaflet (b papillary muscles (c) The points of measurement are set in the middle of the trabeculation The part shown with vertical lines must be deducted from the volume of the ellipsoid. Part with horizontal lines is not included in the volume determination

Bottom left and right A p and lateral projections in systole Symbols the same as above Trabeculation not visible points of measurement are set at outer borderline of ventricular ellipsoid. Papillary muscles are included in the volume i e the short axis on the lateral projection is drawn to the posterior part of the papillary muscle contour As in diastole the subaortic volume (horizontal lines) is not included in the volume determination

tween the long axis and the horizontal plane in the lateral projection is generally slightly larger but is seldom greater than 60 The ventricular ellipsoid is as a rule slightly more pointed towards the heart apex than at the base, in other words it may be said to consist of an upper semi ellipsoid with a slightly lesser degree of eccentricity and a lower one with slightly greater eccentricity This fact does not influence the volume determination as the volume of two united semi ellipsoids with a common contact surface may be calculated by the same method as that used for a regular ellipsoid The factor of greatest significance to the volume measurement is that the two short axis projections in the frontal and lateral projections (*d* and *b*) respectively should always be of approximately the same length This applies to all parts of the heart cycle It means that a section through the ventricle in the plane through the two short axes will be practically circular or in other words that the ventricular ellipsoid is nearly a rotation ellipsoid The ventricle is more irregular in maximum systole than in diastole (see Figs 1c 1d and 2b) and the accuracy of a systolic volume determination is of a much lesser degree than that of the corresponding diastolic value As the main purpose of the method is to determine the stroke volume a percentage error in the determination of the end systolic volume is of relatively less importance than an error in the diastolic volume



a b

Fig 2 *Case I* Athlete's heart No signs of heart disease Pulmonary artery contrast medium injection Films exposed during filling of left side of heart a) Lateral projection end of diastole Small left atrium Mitral leaflets partially visible (→) Top of left ventricular ellipsoid can be traced (↠) b) Lateral projection early phase of diastole Left atrium slightly larger than in late diastole Mitral valve is beginning to open (→) Aortic cusps closed (↠) No trabeculation visible in left ventricle Papillary muscles clearly defined (→) Determination of actual top of left ventricular ellipsoid is difficult

In the cases selected, all measurable pairs of films were subjected to volume calculation, and where possible a volume curve was constructed as well To avoid bias, the stroke and minute volumes were calculated without previous knowledge of the result of the Fick minute volume determination The most important data relating to the material are given in the table on pp 334—335 It does not include the results of clinical examinations and operations, but only a summarizing diagnosis based on clinical and angiocardiographic findings and in some cases on the results of operation

Calculation of left ventricular volume

In an earlier publication (1958) the present writer described the principles for volume measurement when the left ventricle is regarded as an ellipsoid Since that date, however the method has been further developed and simplified In both frontal and lateral projections, it may be observed that in diastole the left ventricle is more or less elliptical in shape (see Figs 1a, 1b, and 2a) In the frontal projection the long axis of the ellipsoid makes an angle usually of between 45 and 55° with the horizontal plane (see Fig 1) The angle be

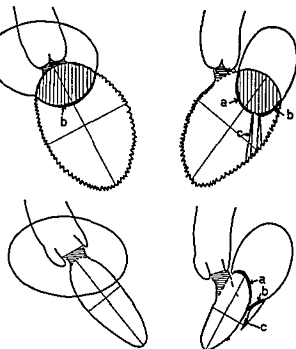


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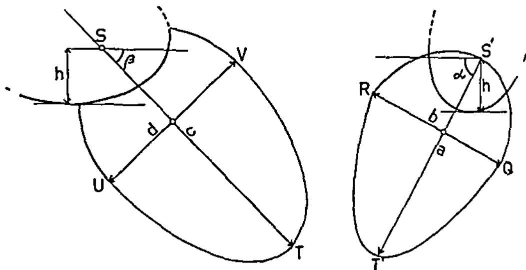


Fig 4 Diagrammatic illustration of the construction of the top of the left ventricular ellipsoid *Left* A p projection showing visible part of left ventricle and bottom of left atrium *Right* Lateral projection showing the same details as in the left figure Height difference *h* mm from bottom of left atrium to top of left ventricle (*S*) is transferred from the lateral to the antero posterior projection At the point where the horizontal line *h* mm above bottom of left atrium in antero posterior projection cuts the long axis projection the top of the ellipsoid is situated (*S*)

In mitral stenosis, the ballooning mitral cusps appear in diastole as a defect in the upper portion of the ventricular ellipsoid (see Figs 1a, 1b and 3) This volume must be regarded as belonging functionally to the atrium as the blood contained between the cusps at the close of diastole will be returned to the atrium at the opening of systole, when the leaflets are thrown back toward the atrioventricular plane (see Figs 1d and 3) Geometrically, the 'balloon' belongs to the left ventricle and consequently the volume of this part must be deducted from that of the ventricular ellipsoid The volume of the space between the mitral valves was calculated partly as an ellipsoid and partly as two segments of a sphere The difference between these two methods of calculation is very small, and the simplest method is to calculate the volume as an ellipsoid The volume of this space varied from 10 to 30 ml In systole, correction for the volume above the mitral valves need not be made when mitral stenosis is present, as during this heart phase the leaflets are thrown upwards and backwards toward the atrioventricular plane and form the upper pole of the ellipsoid (see Figs 1d and 3)

When no mitral stenosis is present, the mitral leaflets are difficult to distinguish and correction for the volume between them cannot be made This volume is very small, however, when the mitral leaflets are normal as they approach each other at the end of diastole The blood immediately under the aortic valves (see Fig 3) will not be included in the volume of the ventricular ellipsoid This space is readily identifiable in the lateral view but not in the frontal view, and

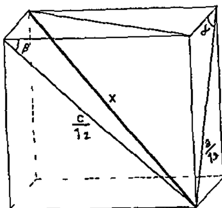


Fig 5 Determination of long axis of left ventricular ellipsoid from the two orthogonal projections which have been corrected for the magnification by dividing by 1 2

hence the volume cannot be calculated satisfactorily This part of the ventricle however does not undergo any appreciable changes during the heart cycle As it is only slightly larger in systole than in diastole it is of little significance in the calculation of the left ventricular stroke volume However owing to the fact that the subvalvular space is not included in the calculation the values for both the maximum and minimum ventricular volumes will be slightly too low

The papillary muscles and trabeculae carneae in the left ventricle constitute another problem in volume measurement As already mentioned GRIBBE et coll (1959) solved this problem in experiments in dogs by determining the volume of these areas of muscle tissue by making models This method is not applicable in man when pathologic conditions are present as the volume particularly in the case of the trabeculae carneae is subject to considerable variations according to the degree of left ventricular hypertrophy The papillary muscles are of little significance in an estimation of the stroke volume as their volume is the same both for end systolic and end diastolic volume calculations (see Figs 1 d and 3) The error arising through inclusion of the papillary muscle volume in the ventricular volume will counteract the error caused by the non inclusion of the subaortic space in the calculation The volume of the trabecular network presents a more difficult problem During the periods of the heart cycle in which the ventricle is of large volume its outer contour is visible at the outer portion of the trabeculation in other words if the ventricular volume is calculated on the basis of the outermost contour, the trabeculae will also be included in the measurement This would not be of much significance if they were also included in the calculation for the heart phases in which the ventricle is small i e at the close of systole This is not the case however as the blood between the trabeculae is pressed out at ventricular contraction and the outer contour of the left ventricular cavity is formed by the inner surface of

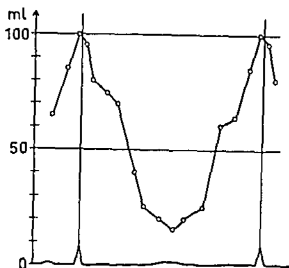


Fig 6 *Case 2* Left ventricular volume curve constructed by plotting together volume determinations from different heart cycles Maximum volume at QRS minimum volume at end of T wave In midphase of systole slightly slower ejection No rapid and reduced ventricular filling during diastole but immediately before atrial systole a slight decrease in the filling speed

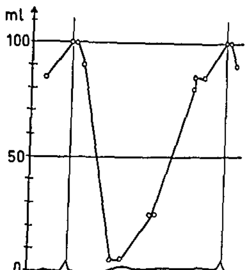


Fig 7 *Case 11* Left ventricular volume curve constructed as in fig 6 Few points of measurement during ejection Small indentation during diastole before left atrial contraction

the trabecular network (see Fig 3) so that the trabeculation will not be included in the ventricular volume at a determination made in the closing phase of systole

The simplest method of compensating satisfactorily for this error is to move in the points of measurement in the roentgen views for a distance equal to half the thickness of the trabecular network This applies only to those views which have been exposed during the phases in which the ventricular volume is large, the thickness of the trabeculation can then as a rule be seen in the films

Volume measurement in practice

As may be seen from Fig 4, the points U, V, R and Q can readily be defined, and the lengths of the two short axis projections *b* and *d* may thus be determined after the thickness of the trabeculation has duly been taken into consideration The points F and F on the antero posterior and lateral projections respectively are as a rule also easy to identify S , which is situated between the mitral and aortic orifices, is usually obtained direct, but in some cases it is necessary to complete the upper part of the ellipse by continuing the outline of the ventricular ellipsoid upwards It is much more difficult to place the point S in the frontal projection, and this can often not be done without an auxiliary construction It is known that the points S and S in the two projections must lie at the same horizontal level If the level of S has been determined in the lateral projection

it can be transferred to the frontal projection if a reference level identifiable in both projections is available. One such level that is usable is the lower border of the left atrium if this chamber has been demonstrated by injection of contrast medium into the pulmonary artery; the radiopaque metal tip of the heart catheter is another excellent reference point in the case of injection into the left ventricle. Fig. 4 will serve as an illustration of this. The point S was obtained through the completion of the lateral ellipse. The difference in height between the lowermost portion of the left atrium and S is h mm. In the frontal view the lower tangent is drawn to the left atrium and a horizontal line is drawn parallel to this line h mm above it. At the point where the upper line meets the longitudinal axis of the frontal ellipse the upper pole of the ellipse will be situated in the frontal projection. The longitudinal axis of the ellipse is constructed by finding the centre point on the transverse axis and drawing the line from the apex out through this centre point. In this way the length of the axis projections may be determined from the long axis in the ellipsoid.

To make further progress with the volume determination it is necessary to know the geometric magnification in the two projections. For the centre of the ellipsoid the magnification in both projections is with the apparatus used approximately 1.2. This is applicable in adult patients in whom the difference in magnification between different individuals is negligible. This means that the two short axes in the ellipsoid are $b/1.2$ and $d/1.2$ respectively. Stereometry must be used in the calculation of the long axis x. In Fig. 5 the frontal and lateral projections of the long axis x have been traced in a parallelepiped after correction for the magnification. It will be found from this figure that

$$x^2 = \frac{a^2}{1.2^2} + \frac{c^2}{1.2^2} \cos^2\beta$$

$$\text{or } x = \frac{1}{1.2}(a^2 + c^2\cos^2\beta)^{1/2}$$

By this procedure the long axis is calculated solely with the assistance of the lengths of the two projections in the frontal and lateral views and the angle formed by the axis projection with the horizontal plane in the a. p. projection. The reason for this method of calculation is that the most difficult axis projection to determine, i.e. axis c, is multiplied by a factor $\cos^2\beta$, which is of the order of magnitude of 0.33 to 0.50; hence the possible error arising in the measuring of c will be reduced. According to the formula for the volume of the ellipsoid the total ventricular volume will be

$$\frac{4\pi}{3} \cdot \frac{1}{1.2 \cdot 2}(c^2\cos^2\beta + a^2)^{1/2} \cdot \frac{b}{1.2 \cdot 2} \cdot \frac{d}{1.2 \cdot 2}$$

$$\text{or } 0.3\, b\, d\, (c^2\cos^2\beta + a^2)^{1/2}$$

Table

Case No	Patient	Age	Sex	Diagnosis	Heart volume total ml	Heart volume ml/m² B S A	Site of contrast injection	L V end diastolic volume ml	L V end systolic volume ml	L V stroke volume ml
1	S J	17	M	Athlete's heart	850	530	LA	105	15	90
2	I B	60	F	Pericardial diverticulum + art hypertension	[1](1 060)	[1](620)	PA	100	15	85
3	I I	14	M	Right sided aortic arch	400	260	PA	60	20	40
4	B T	19	M	Juvenile art hypertension	690	370	PA	130	20	110
5	M K	24	F	Patent ductus postop exam	790	570	LV	80	30	50
6	B T	23	F	Coarctation of the aorta	580	350	LV	50	10	40
7	Å A	27	M	Coarctation of the aorta	770	420	LV	90	40	50
8	K G	43	M	Subaortic stenosis	1 090	550	PA	80	25	55
9	I S	33	F	MS	700	420	LA	95	30	65
10	M C	53	F	MS	820	550	PA	140	25	115
11	S H	49	F	MS	780	510	LA	100	5	95
12	R M	18	M	MS	960	450	LA	95	25	70
13	S I	35	F	MS	910	560	LV	145	45	100
14	M B	33	F	MS	590	380	LV	70	20	50
15	J D	47	M	MS + AoS	1 130	630	PA	130	50	80
16	S A	58	F	MS + AoS	980	430	LV	90	25	65

[1] Diverticulum included in heart volume — [2] Double Fick determination Abbreviations AoS— Aortic stenosis L V — Left ventricle MS — Mitral stenosis PA — Pulmonary artery

In the present work all diameters were measured with an accuracy of 2 mm and the volumes obtained were abbreviated to the nearest 5 ml value The angle β was rounded off to the nearest degree evenly divisible by 5

Control of accuracy of measurement method If the ventricular volume is determined at the end of systole and the end of diastole a value may be obtained for the stroke volume of the left ventricle during the angiocardiographic examination As the heart rate during the examination is known from the simultaneous ECG and exposure recordings, it is possible to determine the minute volume of

Heart rate during angiocardiography	LV minute volume angiocardiographic L	Minute volume Fick determ L	Heart rate during Fick determ	Difference Fick angio minute vol in % of Fick value	Left ventricular volume curve	Pressure PA S/D	PA Mean	PCV Mean	LV	Ao
75	6 8	6 2	80	10	+	23/8 5	14	6		
75	6 4	4.2	76	50	+					
135	5 5	6 5	90	15	—	11/2	6 7	3		
110	12 1	13 2	80	8	—	30 5/12 5	21	13	—	170/90
140	7.0	5 8	62	20	—					
160	6 4	6 5	66	1 5	—	29/8	14	10	173/0—6	208/119
175	8 8	8 6	88	2	—	17/5	12 5	6 5	150/0—4 5	148/98
75	4 1	3 8	6	8	—	31.5/14 7	21	14		
130	8 5	8 8	95	3 5	—	35/17	27	20		
45	5.2	4 7	70	6 5	—	34/10	19	14		
85	8 0	7 2	72	11	+	46/22	33	26		
115	8 0	7 3 7 0	61 66	12 5	—	27 5/7	17	14 5		
64	6 4	6 1	50	5	+	26/9	14	9	100/2 5—9.5	100/49
135	6.8	7 1	8	4	+	43/21 5	29.5	20	117/1 5—7.5	125/67
90	7 2	7 1	85	1.5	—	26/12	18	11		
130	8 5	6 2	68	35	—	30/6	17	9 5	131/0—8	115/57 5

the heart under the prevailing conditions A minute volume determination by the Fick method was carried out in order to ascertain the relation of these values to the true resting minute volume In most of the cases (see Table) there was fairly good agreement between the two determinations especially when it is remembered that even the Fick minute volume determination is considered to be handicapped by an error of ± 10 %

In those cases in which the rhythm is regular during the angiocardiography and which have yielded a number of films with a clearly defined left ventricle the measurement results from different heart cycles may be combined to form

Table

Case No	Patient	Age	Sex	Diagnosis	Heart volume total ml	Heart volume ml/m² B S A	Site of contrast injection	LV end diastolic volume ml	LV end systolic volume ml	LV stroke volume ml
1	S J	17	M	Athlete's heart	850	530	PA	105	15	90
2	L B	60	F	Pericardial diverticulum + art hypertension	[1](1 060)	[1](620)	PA	100	15	85
3	I L	14	M	Right sided aortic arch	400	260	PA	60	20	40
4	B T	19	M	Juvenile art hypertension	690	370	PA	130	20	110
5	M K	24	F	Patent ductus postop exam	790	570	LV	80	30	50
6	B T	23	F	Coarctation of the aorta	580	350	LV	50	10	40
7	A A	27	M	Coarctation of the aorta	770	420	LV	90	40	50
8	K G	43	M	Subaortic stenosis	1 090	550	PA	80	25	55
9	I S	33	F	MS	700	470	PA	95	30	65
10	M C	53	F	MS	820	550	PA	140	25	115
11	S H	49	F	MS	780	510	PA	100	5	95
12	R M	18	M	MS	960	450	PA	95	25	70
13	S L	35	F	MS	910	560	LV	145	45	100
14	M B	33	F	MS	590	380	LV	70	20	50
15	J D	47	M	MS + AoS	1 130	630	PA	130	50	80
16	S A	58	F	MS + AoS	980	430	LV	90	25	65

[1] Diverticulum included in heart volume — [2] Double Fick determination Abbreviations AoS — Aortic stenosis LV — Left ventricle MS — Mitral stenosis PA — Pulmonary artery

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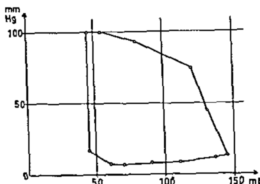


Fig 10 *Case 13* Pressure volume diagram constructed from the volume curve in fig 9 and the pressure curve from left ventricle recorded before angiocardiography Systole begins at bottom right. First part early systole large pressure increase small volume decrease. Second phase of systole small pressure increase large volume decrease Top left end of systole. Vertical line to the left isometric relaxation Bottom line volume increase during diastole very slight pressure increase Integrated area within left ventricular working line corresponds to 0 93 joule

for those cases from which a left ventricular volume curve has been obtained and when a pressure curve from this ventricular chamber taken at the same heart rate is also available Owing to the fact that in most of our cases the rhythm was different at the pressure recording and at angiocardiography only two such diagrams could be made Naturally the ideal procedure would be to carry out the pressure recording and angiocardiography simultaneously but this involves considerable technical problems A pressure diagram from our Case 13 is shown in Fig 10 It is possible from such a diagram to obtain a relative value for the volume pressure work of the left ventricle by integration of the area within the working line (cf KATZ) This method is still at the experimental stage

Discussion

The method described for angiocardiographic determination of left ventricular stroke volume is intended to be usable for quantitative calculation of the degree of mitral or aortic insufficiency a subject to be discussed in a future publication In order to assess the applicability of the method a material of patients without insufficiency of the mitral or aortic orifices was assembled for the present work

As seen from the description of the procedure the angiocardiographic examination takes place under completely unphysiologic conditions Although such factors as general anaesthesia increased intrabronchial pressure and injection of contrast medium are introduced it has been found that a fairly good agreement exists between an angiocardiographic minute volume determination and one carried out by the Fick method, this applies even if the rhythm at angiocardiography is much higher than at a Fick determination From this it is evident that the increased cardiac rate at angiocardiography is not due to an increased venous return as if this were so the minute volume would be increased The volume curves that could be made for the left ventricle to some extent

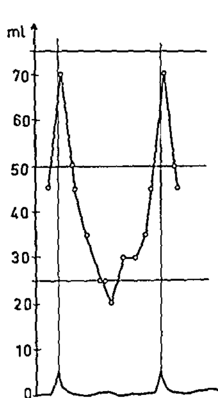


Fig. 8. *Case 14.* Left ventricular volume curve. Tachycardia during examination 135 *strokes* per min. Evacuation of ventricle very rapid during early systole. *Diastole is short and most of the ventricular filling takes place during atrial systole.*

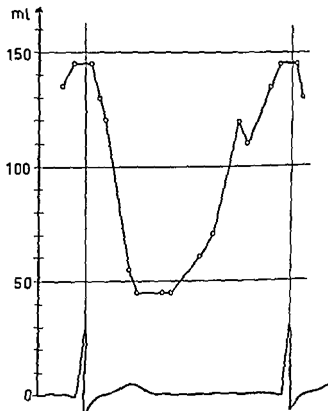


Fig. 9. *Case 13.* Left ventricular volume curve. Relatively slow heart rate during examination. No exposure obtained at QRS and maximum volume is probably lacking. During late systole the curve is flattened. Note indentation in diastole before P wave.

a volume curve (LVC) giving a graphical representation of how filling and evacuation of the left ventricle takes place during the heart cycle. Curves obtained from the material have been included in order to demonstrate that the method of measurement is sufficiently accurate to produce a satisfactory curve and that views from different cycles in the same heart phase give approximately the same volume values (see Figs 6 to 9).

These volume curves, which will not be discussed in detail here, are of great interest from the theoretical haemodynamic standpoint. It is possible to obtain information from them regarding variations in ejection rate in different phases of systole. By determination of the cross section of the aorta, which is easy to carry out with angiocardiography, a value for the velocity of the blood flow in the ascending aorta may be obtained. It is also possible to study how left ventricular filling is affected by mitral stenosis and by atrial systole.

Construction of a pressure volume diagram for the left ventricle. A diagram illustrating the volume/pressure conditions in the left ventricle may be drawn

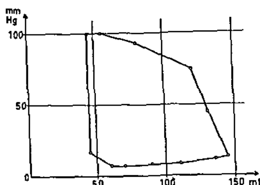


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provide new aspects on left ventricular filling and evacuation In general it may be said that the curves are not suitable for a study of small details, owing mainly to two factors, namely that a continuous course has been recorded with a discontinuous method, and that the error of the method is too great to permit definite conclusions to be drawn from small irregularities in the curve However, the volume maximum can always directly be connected with the QRS complex in the electrocardiogram The volume minimum is situated approximately at the end of the T-wave, and as a rule there is a plateau at the close of systole An important practical conclusion may be reached from these observations, namely, that for the calculation of the stroke volume it is only necessary to determine the volume from two pairs of films, one pair exposed at the QRS complex and the other at the end of the T-wave This means that in routine determinations of the stroke volume the work can be carried out relatively rapidly without time consuming measurement of the whole series of films

SUMMARY

Biplane angiocardiography was used to determine left ventricular volume in different phases of the heart cycle The stroke volume in the left ventricle was determined from the maximum and minimum left ventricular volumes and the minute volume during angiocardiography was then determined from the stroke volume and cardiac rate The minute volume determinations at angiocardiography and by Fick s technique were compared

ZUSAMMENFASSUNG

Die biplane Angiokardiographie ist zur Bestimmung des linken Herzkammervolumens in verschiedenen Phasen des Herzzyklus benutzt worden Das Schlagvolumen des linken Ventrikels wurde aus dem hochsten und dem niedrigsten Volumen bestimmt Danach wurde das Minutenvolumen wahrend der Angiokardiographie aus dem Schlagvolumen und der Frequenz der Herzkontraktionen bestimmt Die Bestimmungen des Minutenvolumens bei der Angiokardiographie und mit der Fick Technik wurden miteinander verglichen

RÉSUMÉ

L angiocardiographie bidirectionnelle a été utilisée pour déterminer le volume du ventricule gauche à différentes phases du cycle cardiaque Le volume systolique du ventricule gauche a été déterminé d après les volumes ventriculaires gauches maximum et minimum et le débit par minute au cours de l angiocardiographie a été déterminé à partir du volume systolique et du rythme cardiaque Les mesures du débit par minute obtenues par angiocardiographie et par la technique de Fick ont été comparées

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF OLLE OLSSON) AND THE GYNAECOLOGIC DEPARTMENT OF THE RADIOTHERAPEUTIC CLINIC (DIRECTOR G GORTON), UNIVERSITY HOSPITAL OF LUND, SWEDEN

INGUINAL AND PELVIC LYMPHOGRAPHY

A preliminary report

by

W A FUCHS and G BOOK HEDERSTROM

The roentgenographic demonstration of the lymphatic system has been increasingly used in recent years as a method of detecting malignancy in lymph nodes

TJERNBERG (1956) studied in animals experimentally induced inflammatory changes and tumor metastases in lymph nodes FISCHER & ZIMMERMANN (1959) investigated tumor simulating lesions and inflammatory reactions, produced artificially in the lymph nodes of animals, by means of lymphography COLLETTE (1958) presented the first and up to then the largest clinical study of human subjects with cancer metastases in the pelvic lymph nodes investigated lymphographically KAINDL et coll (1958, 1960) believed they found characteristic roentgenographic changes in lymph nodes for different types of malignant tumors MALAMOS et coll (1959) described structural changes in malignant systemic diseases of the lymph nodes MALEK et coll (1958, 1959,) studied in animals the physiologic aspects of direct and indirect lymphography as well as inflammatory changes of lymph nodes BRUUN & ENGESET (1956), PROKOPEC & KOLINOVA (1958) and ZHEUTLIN & SHANBROM (1958) injected oily contrast medium percutaneously into lymph node tumors SHEEHAN et coll (1961) and WALLACE et coll (1961) performed direct lymphography with an oily contrast medium in human subjects and obtained a filling of the aortic lymph nodes and even the thoracic duct COLLETTE (1958) and FUCHS et coll (1960) demonstrated by lymphography tumor involvement of the lymph nodes in the pelvic region as a cause of chronic secondary lymphedema

Submitted for publication 12 May 1961







F g 1 N rmal ing n l and pel ic lymphograms Inferior superficial inguinal lymph nodes (1) deep inguinal lymph nodes (2) superficial lateral xternal iliac lymphatic group (3) deep later l external liac lymphatic group (4) medial external iliac lymphatic group (5) lateral c mmon il c lymphat c grou p (6) medial common il ac lymphatic group (7) aort c lymphatic group (8)

FROM THE ROENTGENDIAGNcally some of the findings reported by these authors
AND THE GYNAECOLOGICpractical value of lymphography in tumor diagnosis,
RECTOR G GO a series of patients with probable malignancy of the
ly the pelvic lymph nodes We present a preliminary re
based upon the results of 94 lymphographies performed in 65

Technique

filling of the inguinal lymph nodes is relatively easy by the injec
to 5 ml contrast medium into a lymph vessel on the dorsum of the foot
KINMONTH method Because of the resistance to the lymph flow and con
ently to the passage of the contrast medium in the inguinal lymph nodes
nonstration of the lymphatic system in the pelvic region is far more difficult
o achieve Following a suggestion by COLLETTE (1960) we use an automatic injection apparatus and inject 15 to 30 ml contrast medium Starting at a low speed so as to distend the lymph vessel, the injection rate is gradually increased so that all the contrast medium is injected in about 10 minutes The automatic injection apparatus recently described by CLEMENTZ & OLIN (1961) assures a constant rate of flow and one which may easily be controlled To prevent retroextravasation of contrast medium at the site where the puncture needle penetrates the wall of the lymph vessel a silk ligature is placed around the needle While injecting the contrast medium a series of 6 to 8 roentgenograms of the inguinal and pelvic region is taken at intervals of about 30 seconds The exposures are made as soon as a burning sensation up through the leg to the inguinal region, produced by the injected contrast medium, is felt by the patient Roentgenograms taken later than 10 minutes after the beginning of the injection of the water soluble medium show blurred lymphatic structures due to extravasation The exposures are made with the patient with the side to be investigated rotated slightly externally and, for the last roentgenogram, marked ly rotated We normally obtain contrast filling of the lymphatic system up to the level of the upper part of the sacrum and in some cases as high as the lumbar region

No evidence of lymphedema due to the investigation was observed in our material and no complications, other than an infection at the incision site in one case, were recorded The contrast media used for our series of investigation were all water-soluble, namely Urografin 60 % and 76 % and Biligrafin forte The two latter demonstrate the lymphatic vessels and lymph nodes with a higher contrast density, but no difference in their tendency to diffuse through the walls of the lymphatic was evident, the quality of the roentgenograms was essentially the same with both types of contrast media The burning sensation experienced by the patients varied widely but was most marked with Uro grafin 76 % The use of oily contrast media for intralymphatic injection seems not to be without risk Necrosis and lipogranulomatous reactions in the lymph

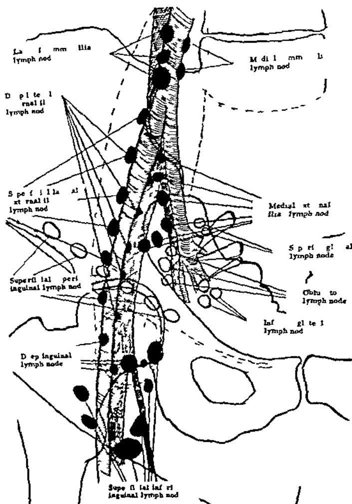


Fig 2 Schematic drawing of the inguinal and pelvic lymph nodes *Black* Lymph nodes demonstrated by lymphography *White* Lymph nodes not shown by lymphography

nodes investigated due to damage by the contrast medium have been described (Bennett & Shivas 1954 Engeset 1958 Fischer & Zimmermann 1959 Wallace et coll 1961) The risk of fat embolism in the lungs has to be considered (Engeset 1958 Wallace et coll 1961) Malek et coll (1959) demonstrated in animal experiments that water soluble contrast media that have a tendency to remain in the lymphatic system for a relatively long period of time show a tendency to damage the lymph nodes proportional to their duration of stay in the lymphatic system These authors state that water



Fig. 3. Normal lymph nodes in different stages of contrast filling. a) Early stage of filling. Only the afferent vessels of a superficial inguinal lymph node are filled (→). b) Late stage of filling. The lymph node is now entirely filled with medium (++). A large number of superficial and deep inguinal lymph nodes are present.

soluble contrast media may stay in the lymphatic system for up to one hour and described necrotic and fibrotic changes followed by blockage of the lymphatic system and subsequent lymphedema. Since oily contrast media remain in the lymph nodes for a period of several months, further animal experiments must be carried out to determine whether they may be considered as being innocuous to the lymphatic system.

Roentgen anatomy

The nomenclature and roentgen anatomy of the lymph vessels and lymph nodes in our series of investigations is based mainly upon the classic anatomic studies of Barthels (1909) and Jossifow (1930) as well as upon the careful in



Fig 4 Different types of normal superficial inguinal lymph nodes

vestigations of REIFFENSTUHL (1957) The roentgen anatomic descriptions by COLLETTE (1958), KAINDL et coll (1958 1960) GERGELY (1958) JACOBSSON & JOHANSSON (1959) MALEK et coll (1959), FUCHS et coll (1959), DEL BUONO et coll (1959) and WELIN & JOHANSSON (in print) have also been considered

The injection of contrast medium into the medial and in some cases the lateral group of subcutaneous lymphatics on the dorsum of the foot, regularly produces a characteristic appearance of the lymph vessels and lymph nodes in the inguinal and pelvic regions (Fig 1) The medial and lateral group of sub cutaneous lymphatics of the leg drain mainly into the same group of one to four inferior superficial inguinal lymph nodes A few lymphatics may run directly to the deep inguinal or even to the pelvic lymph nodes The numerous afferent vessels of the inferior superficial inguinal lymph nodes are normally fine and divide into several branches before entering the sinus of the lymph nodes their efferent lymphatics fill as an inconstant finding some tiny deep inguinal lymph nodes These efferent vessels are coarse and often have nu merous valves and they follow the external iliac artery in two main groups of lymphatics namely the lateral external iliac and the medial external iliac groups The former is situated laterally to the external iliac artery and com prises a group of two to six lateral external iliac lymph nodes of various sizes This group of lymphatics is divided into a superficial and a deep section The former is situated ventrally and the latter dorsally to the external iliac artery Because of the great anatomic variation both or only one of these may be pres ent and thus filled with contrast medium When only one section is present it is difficult to judge whether it is the superficial or the deep The efferent lymphatics of the lateral external iliac lymph nodes are called lateral common iliac and include some small lymph nodes of the same name Some of these efferent lymphatics form a constant connection to the medial external iliac group of lymphatics and lie dorso-medially to the external iliac artery, they include several medial external iliac lymph nodes mainly of small calibre connected by a network of wavy anastomosing lymphatics In the sacro iliac



Fig 3 Normal lymph nodes in different stages of contrast filling a) Early stage of filling Only the afferent vessels of a superficial inguinal lymph node are filled (→) b) Late stage of filling The lymph node is now entirely filled with medium (⇸) A large number of superficial and deep inguinal lymph nodes are present

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Fig. 5. a) Normal superficial inguinal lymph node with fibrosis and fatty involution of its centre. b) Conglomeration of several small superficial inguinal lymph nodes (verified histologically). c) Lymphosarcoma (generalized in a 63 year old man). Enlarged superficial inguinal lymph nodes with rounded filling defects and slightly irregular contours (verified at autopsy).

region this group is called, because of its relationship to the common iliac artery, the medial common iliac group of lymphatics. The lateral and medial groups of iliac lymphatics are to a great extent superimposed in roentgenograms obtained in a true frontal projection. The two groups may be seen more distinctly when the patient is turned towards the side being investigated; pelvic and inguinal lymphograms should therefore be obtained as a routine procedure in this position.

We obtained filling of the aortic lymph vessels and lymph nodes in some cases; however, a description of the lymphatic system of this region would be incomplete and premature at the present time.

Injection of contrast medium into the dorsal group of lymphatics does not give the same satisfactory results; the small number of lymphatics filled drain into a single deep inguinal or pelvic lymph node.

An exact knowledge of the topography of the lymph nodes accessible to the present technique of lymphography and of the regional lymph nodes, where metastases from a cancerous pelvic organ may be expected, is of utmost importance (Fig. 2).

We have studied the relationship between the different groups of lymphatics and the various pelvic arteries by carrying out simultaneous pelvic lymphography and arteriography as well as by localizing the various groups of lymph nodes by extraperitoneal lymph node excision (GORTON 1953, 1957).

The more medially located pelvic lymph nodes as well as the numerous superior inguinal lymph nodes cannot be demonstrated roentgenographically by the present technique. The presence of a large number of lymphatics con



ig 6 Squamous cell carcinoma n a 76-ea -old man w th local recurrences n the nguinal reg on after surgical exc s on of the malignant inguinal and pelv c lymph nodes Pr mary tumor unknown



a



b

Fig 7 Chronic lymphadenitis in a 15 year-old boy with secondary lymphedema of right leg Enlarged superficial inguinal lymph nodes w th numerous rounded fill ng defects in ea ly stage of filling (a) due to enlarged lymph follicles Blurred structural pattern of the lymph node n late stage of filling (b) due to d ffusion of the contrast med um

necting the different inguinal and pelvic lymph nodes increases however the possibility of detecting early malignancy by lymphography The centrifugal direction of the lymph flow from the various pelvic organs ensured by the nu merous valves in the lymph vessels makes it impossible to produce a retrograde circulation so as to obtain contrast filling of the more medially located lymph nodes Although the basic pattern of lymph vessels and lymph nodes filled in the inguinal and pelvic regions is constant a great number of individual varia tions are encountered this must be taken into account when considering the differential diagnostics

Considerable variation in the normal structural pattern of superficial inguinal lymph nodes may be observed Diffusion of the water soluble contrast medium in the course of the investigation obscures small filling defects produced by lymph follicles small inflammatory lesions and tumor infiltration (TJERNBERG 1956 COLLETTE 1958 FISCHER & ZIMMERMANN 1959 MALEK et coll 1959) The contrast medium often passes in the first stage of the investigation directly from the afferent to the efferent lymph vessels of a lymph node without the parenchyma of the lymph node as a whole being demonstrated It is only the continuous flow of contrast medium which provides a complete filling of these lymph nodes in the later stages of the investigation the structural pattern of the nodes therefore to some degree changes Lymphograms can thus only be



Fig 8 Reticulosarcoma (generalized in a 41 year-old man) Large inguinal and pelvic tumor masses (→)

judged with accuracy in serial films which demonstrate the different stages of contrast filling (Fig 3) Roentgenograms taken at the end of the contrast injection show only blurred and indiscernible lymphatic structures which makes an appropriate diagnosis practically impossible (Figs 3 and 7)

A wide range of variation of the structural pattern was present in a large series of patients with no clinical signs of pathologic changes in the inguinal lymph nodes (Fig 4) The histologic studies of some of these lymph nodes led us to assume that all these structural variations represented normal abnor



Fig 9 Lymph node metastasis in a 33 year-old woman with carcinoma of the cervix uteri stage III infiltrating the vagina and urethra but not the parametrium Enlarged lateral external iliac lymph node with numerous small rounded filling defects but regular contours (→) (Verified at operation)



Fig 10 Total blockage in a 43 year-old woman with carcinoma of cervix uteri stage II infiltrating upper part of vagina but not the parametrium Total obstruction of medial external iliac lymphatic group (→) due to metastases in medial external iliac lymph nodes Collateral circulation through lateral external iliac lymphatic group (↔) (Verified at operation.)

malities The replacement of the central part of the lymphoid tissue by fatty and connective tissue in inguinal lymph nodes of elderly patients a fact recognized by pathologists is clearly demonstrated by lymphography (Fig 5a) A conglomeration of several small lymph nodes may sometimes hardly be differentiated from a single large inguinal lymph node (Fig 5b)



Fig 8 Reticulosarcoma (generalized in a 41 year old man) Large inguinal and pelvic tumor masses (→)

judged with accuracy in serial films which demonstrate the different stages of contrast filling (Fig 3) Roentgenograms taken at the end of the contrast injection show only blurred and indiscernible lymphatic structures which makes an appropriate diagnosis practically impossible (Figs 3 and 7)

A wide range of variation of the structural pattern was present in a large series of patients with no clinical signs of pathologic changes in the inguinal lymph nodes (Fig 4) The histologic studies of some of these lymph nodes led us to assume that all these structural variations represented normal abnor



a b

Fig 12 Lymph node metastasis in a 44 year old woman with carcinoma of the cervix uteri stage III infiltrating the parametrium Enlarged lateral external iliac lymph node with irregular contours and filling defect in peripheral parts of lymph node due to tumor infiltration (→) (Verified at operation)

different types of normal and pathologic structural patterns of inguinal and pelvic lymph nodes

The presence of malignant primary tumors of the lymphatic system may however be diagnosed with some certainty when the lymph nodes are considerably enlarged and present a structural pattern far removed from the normal Lymphography in such cases affords valuable information about the site and extent of the massive lymphomas which is often not possible by other means of investigation (Fig 8) In cases in which the nature of an expansive process cannot be diagnosed clinically, its contrast filling will demonstrate its association with the lymphatic system

Early metastatic involvement of regional lymph nodes may be shown by means of lymphography when clinical signs of metastatic spread are absent or only probable

In a patient with carcinoma of the cervix uteri stage III infiltrating the vagina and urethra but not the parametrium lymphography showed an enlarged lateral external iliac lymph node with numerous small rounded filling



Fig. 11. Total blockage due to tumor infiltration in a 42 year old woman with carcinoma of the cervix uteri stage III infiltrating the parametrium. Non functioning left kidney at urography. Total obstruction of distal part of medial external iliac lymphatic group (→). Collateral circulation through the lateral external iliac group of lymphatics (↔). Lymph node metastasis in a lateral external iliac lymph node.

Diagnosis of pathologic changes

Accurate diagnosis of primary tumors and early metastases in pelvic and inguinal lymph nodes is one of the most important goals of pelvic and inguinal lymphography. Differentiation between normal and pathologic findings especially in these early states of tumor involvement, is often most difficult.

Normal inguinal lymph nodes (Figs 3, 4 and 5 a—b) and inguinal lymph nodes of patients with lymphosarcoma (Fig. 5c), lymphogranuloma, squamous cell carcinoma (Fig. 6), and chronic non specific inflammation (Fig. 7) may resemble each other to a very high degree. With due regard to this fact we are inclined to believe that a definite diagnosis of the different forms of lymph node tumors is hardly possible by means of lymphography. Further investigations are being carried out with a view to obtaining more information on the

SUMMARY

The different patterns of the normal roentgen anatomy of the inguinal and pelvic lymphatic system demonstrated by automatic injection of a water soluble contrast medium are described The diagnostic problems of inguinal and pelvic lymphography are discussed particularly in respect to the value of the method for an early detection of primary tumors and metastases

ZUSAMMENFASSUNG

Die verschiedenen Aspekte der normalen Rontgenanatomie der Leisten und Beckenlymph knoten werden demonstriert Ihre radiologische Darstellung gelingt durch automatische In jektion von wasserloslichem Kontrastmittel Mehrere diagnostische Probleme der inguinalen und pelvinen Lymphographie werden diskutiert besonders im Hinblick auf den Wert der Methode fur eine Fruhdiagnose von Primartumoren und Tumormetastasen

RÉSUMÉ

Les aspects normaux de la chaine ganglionnaire inguino-ilio-pelvienne sont présentés Leur mise en évidence est effectuée par injection d un produit de contraste hydrosoluble au moyen d une seringue automatique Plusieurs problemes diagnostiques de la lymphographie in guinale et pelvienne sont discutés L accent est spécialement mis sur la valeur de cette méthode pour le diagnostic précoce des métastases ganglionnaires des tumeurs pelviennes et des lymphomes malins

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defects but regular contours (Fig 9) The diagnosis of metastatic involvement was made and subsequent operation showed a metastatic lymph node tumor attached to the psoas muscle

Another patient with carcinoma of the cervix uteri, stage II, infiltrating the upper part of the vagina, presented on lymphography total blockage of the medial external iliac group of lymphatics with collateral circulation over the lateral external iliac group of lymphatics Extraperitoneal lymph node excision revealed metastatic involvement of the medial external iliac lymph nodes (Fig 10)

Similar findings of obstruction may also be present in cases of direct malignant infiltration of the parametrium (Fig 11) Enlarged lymph nodes with irregular contours produced by filling defects in the peripheral parts of the lymph nodes due to tumor infiltrations may be mistaken for metastases These changes may be evaluated more accurately by obtaining roentgenograms in different projections (Fig 12)

Normal lymphographic findings do not exclude tumor involvement of lymph nodes in the pelvic region not accessible by the present technique of investigation In a case of carcinoma of the cervix uteri, stage I, no pathologic changes in the lymphatic system filled at lymphography could be detected but metastases in the obturator lymph nodes, which are not filled with contrast medium by the present lymphographic technique, were found later at extraperitoneal lymph node excision

Conclusions

Contrast filling of inguinal and pelvic lymph nodes may be achieved best by automatic injection of large quantities of a water soluble contrast medium Serial roentgenograms in different projections give the most dependable diagnostic results Knowledge of the topography and the roentgen anatomy of the inguinal and pelvic lymph nodes, as well as the lymphatic drainage of the various pelvic organs, are of utmost importance for accurate diagnosis

Normal inguinal lymph nodes present a great variation of structural patterns It is often difficult to distinguish these from pathologic changes

Primary tumors and metastases in pelvic and inguinal lymph nodes, which cannot be approached clinically, may be demonstrated by means of lymphography

A certain number of inguinal and pelvic lymph nodes cannot be filled with contrast medium by the present technique of lymphography Normal lymphographic findings do thus not exclude malignancy of inguinal and pelvic lymph nodes

FROM THE RADIOLOGICAL INSTITUTE (DIRECTOR PROF G G PALMIERI) OF BOLOGNA UNIVERSITY ITALY

ANGIOCARDIOGRAPHIC DEMONSTRATION OF THE VALVES OF THE AZYGOS VEIN IN TRICUSPID STENOSIS

by

G TORI and G F GARUSI

The valves of the azygos vein are situated in the middle or posterior third of its arch and are usually two in number Three valves or only one valve, may occasionally be present when single the valve is always rudimentary (SYLWANOWICZ)

We have been able to demonstrate the anatomical details of the valves during angiocardiography in cases of reflux of contrast medium into the azygos vein, or after the intraosseous injection of contrast medium The cusps of the valve, which are mostly double and face forwards become visible as contrast medium fills the valvular pockets Being at the level of the so called intermediate part of the azygos arch the valves are projected axially by the roentgen beam producing a 'coffee bean appearance The halves of the bean which are almost rounded in shape correspond to the two contrast filled pockets and the central separating line represents the slit between the two cusps (Fig 1a) The edges of the valves vary in position and size (Fig 1b) They are best seen at reflux in the antero posterior projection but may also be visible in the lateral projection sometimes only as bulges in the vein In frontal roentgenograms the valves are generally superimposed upon the superior vena cava (Fig 2a) but may also be projected outside it as dependent on the shape and position of the inter mediate part of the arch of the azygos vein (Fig 2b) If the valves lie in the posterior third of the arch which pursues a medio lateral course the valves will be seen from the side instead of from an axial direction, or more or less obliquely producing what we have termed snake jaws appearances (Fig 3)

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Fig 3 Snake jaws image of the valvular apparatus of the arch of the azygos vein in a case of tricuspid stenosis associated with mitral disease

Fig 4 The valves of the arch of the azygos vein in two orthogonal simultaneous projections in a case of tricuspid stenosis The cusps which have a pointed contour in a lateral projection suggest competence

The images described are produced by more or less competent valves as may be seen more clearly in the lateral views of Figs *4 and 5* *in which the* edges of the valves appear pointed or rounded in shape We *have encountered such* valve images particularly in cases of retarded emptying of the right atrium due to tricuspid stenosis although *we have not* been able to demonstrate them in all such cases These features have been observed after injection of the *contrast medium* through a catheter with the tip placed in the right atrium (Fig 6) as well as after injection into the brachial vein The valves have not been visible in *cases of* moderate reflux of contrast medium from the superior vena cava into the azygos vein or in cases in which the reflux has been so marked that the whole arch and a small part of the ascending tract of the azygos vein have been filled The coffee bean appearances persist for some 10 to 15 seconds after the injection

We have observed reflux into the azygos vein from the vena cava in numerous cases of mitral valve disease with moderate stasis and no involvement *of the* tricuspid valves but the valves have never been visible in such cases They have very rarely been observed in congenital defects with hypertension of the right cavities of the heart (tetralogy of Fallot) (Fig 5)

a b

Fig 1 Valves of the arch of the azygos vein *during angiocardiography* in two cases of tricuspid stenosis a) Coffee bean image with equal borders b) The borders are unequal in size and differently placed In *both* cases *the* contrast medium is retained in the post valvular pockets



a b

Fig 2 Valves of the arch of the azygos vein and their relation to the superior vena cava in a further two cases of tricuspid stenosis The image of the post valvular pockets is projected within the superior vena cava (a) and outside it (b)







a b

Fig 6 Severe tricuspid stenosis studied with selective angiocardiography Typical "coffee bean" image of the azygos valves obtained obviously through reflux

Fig 7 The valvular image of the azygos vein in cases without right endo-atrial stasis a) Coarctation of the aorta with lateral displacement of the superior vena cava due to a dilated ascending aorta b) Mediastino-pulmonary tumour with displacement and probably infiltration of the superior vena cava

defects with hypertension of the right heart, and of mitral and tricuspid defects alone or in combination with other diseases, that the radiologic visibility of the valvular system of the azygos vein in the a p projection constitutes an important sign of prolonged stasis in the right heart due mainly to tricuspid stenosis The sign is however not pathognomonic as we have observed three cases without high pressure in the right atrium One of these was a case with coarctation of the aorta and the other two were cases of mediastino pulmonary tumours (Fig 7)

The value of the finding described which is frequent in tricuspid stenosis (14 out of our 20 cases) is in our opinion not invalidated by the existence of the aforementioned three cases (out of a material of 250 angiocardiographies) It is possible that in these three cases without increased pressure in the right atrium lateral displacement or compression of the superior vena cava may have caused the valve images to appear

SUMMARY

The angiocardiographic appearances of the valvular system of the arch of the azygos vein are described The visibility of the valves is particularly frequent in cases of tricuspid stenosis



Fig 5 Example of competence of the valvular cusps of the azygos vein in a case of tetralogy of Fallot The cusps appear rounded in the lateral projection (b)

It is not easy to explain how this filling of the valvular pockets is produced It is above all necessary for the reflux to reach the valvular system and for the valvular pockets to be enlarged, but we have not been able to find any relationship between the degree of enlargement of the superior vena cava and the post valvular segment of the azygos vein and the morphology of the valvular system During the initial phase of inspiration, the pressure within the superior vena cava is negative and then gradually becomes positive, this might produce a persistent reflux from the vena cava into the azygos vein, for which the determining factor on the other hand must be the existence of a considerable rise in pressure in the right atrium In addition to the reflux into the azygos vein, there was in almost all of our cases of tricuspid stenosis a more or less marked reflux of contrast medium into the first part of the inferior vena cava and some of the hepatic veins

Conclusions

The valvular system of the azygos vein, situated in the middle or posterior third of the azygos arch, taken in axial direction by the roentgen beam in a p projection, produces characteristic images Its filling is often of long duration It appears from a study of our angiocardiographic material of congenital

FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR DOCENT U RUDHE) OF THE PAEDIATRIC CLINIC KAROLINSKA SJUKHUSET STOCKHOLM SWEDEN

INJURIES OF THE CARPAL SCAPHOID IN CHILDREN

by

HERBERT MUSSBICHLER

It has previously been considered that fractures of the carpal scaphoid are rare in children (RETTIG BLOUNT EHALT) It would appear to us however that such fractures are not uncommon and that our roentgendiagnostic experiences of scaphoid injuries in children under 15 years of age may be of interest The patients were examined and treated in our clinic during the years 1952 to 1960

Material and Methods In addition to the usual views (Figs 1 and 2) frontal lateral and lateral oblique (a position midway between pronation and supina tion with the hand slightly flexed dorsally and deviated toward the ulna) we have also used a projection with the hand in more or less extreme pronation (Fig 3) giving tangential views of the dorsoradial surface of the scaphoid bone (Figs 1 2 5 6 7) Films without intensifying screens were used

Among 3 406 children under 15 years of age referred for roentgen examina tion of the hand or wrist there were 107 with roentgenologic evidence of damage of the carpal bones 100 of these had a fracture through the scaphoid bone and these cases were used as the material for the present study The distribution of different types of fracture in adults and children as ascertained from the literature as well as from our own series is presented in the Table on p 362 while the Diagram p 363 shows the distribution over different age groups

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ZUSAMMENFASSUNG

Das angiokardiographische Aussehen des Klappensystemes des Bogens der Vena azygos wird beschrieben Die Sichtbarkeit der Klappen ist in Fällen mit Trikuspidalklappenstenose besonders häufig

RÉSUMÉ

Les auteurs décrivent l image angiocardiographique du système valvulaire de la crosse de l azygos La visibilite des valvules est particulièrement fréquente en cas de sténose tricuspidienne

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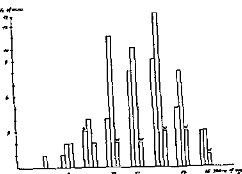


Diagram showing the number types and location of fractures of the scaphoid in relation to the age of the patients A — avulsions D — distal parts W — waist of scaphoid

The position and shape of this recess corresponded to the area of increased density in the soft tissues which was consistently found in our material of scaphoid fractures and which thus appeared to be due to exudation into the joint capsule recess near the scaphoid bone The occurrence of exudation in this recess was also studied in conventional views of the wrist and carpal bones in cases with other lesions in and around the wrist joint Exudation was observed in all 7 cases with fractures in other carpal bones as well as in a few cases with contusion of the back of the hand At the same time only one exudation was encountered in 10 cases with epiphysiolysis of the radius and there was no exudation among 20 radius fractures some of which were combined with detachment of the styloid process of the ulna In these cases swelling of the external soft tissue not to be confused with an exudation into the joint capsule was sometimes present (Fig 8)

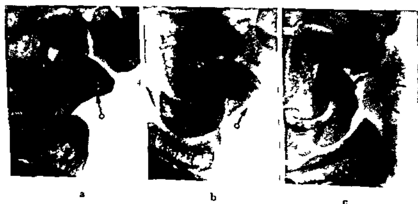


Fig 1 Lateral oblique lateral and pronation views showing the line of fracture from the volar (tubercle o→) to the dorso radial aspect (↦) Expansive swelling of the joint capsule recess (→)

Table

Frequency and location of carpal scaphoid fractures in children and adults

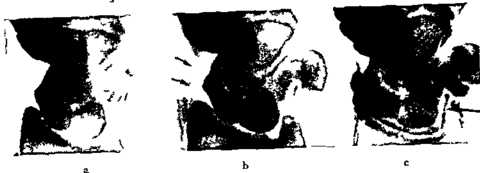
	Authors	Number of fractures	Proximal	Waist	Distal	Avulsions at radial dorsal aspect
In adults	ANDERSEN and THERKELSEN	135	25	55	55	
	RUZICKA and HRUBLEIN	16	6	8	2	
	TROJAN	873	141	513	219	
In children	MÜSSBICHLER	100	—	15	33	52

Results

In our material, fractures were observed on the medial and distal but not on the proximal part of the scaphoid Forty eight cases had fractures and fissures of the type commonly seen in adults, in the remaining 52 cases the fractures were of a different appearance, the characteristic feature being that one or more fragments had become detached from the dorsoradial surface of the scaphoid distal to its centre (Figs 2, 5, 6, 7) In 6 of these cases, transverse fractures of the distal part were also observed The fragments were best seen in the ordinary frontal projection or in films taken with the hand in pronation Only in a few cases were they visible in the lateral oblique position, and in none in the lateral projection As films in the pronation position were not consistently obtained in the present series the incidence of avulsion of small fragments was probably greater than has been indicated

Control examinations In 30 children with avulsions who were treated with a plaster cast or a plaster splint for 2 to 3 weeks and followed up, the healing time was 3 to 6 weeks, in the group with fractures and fissures through the medial and distal parts of the scaphoid healing took place within 4 to 7 weeks Pseudo arthrosis was observed in two neglected cases As in the case of adults, increased density in the fracture area, indicating endosteal callus formation, was observed during the healing of the transverse fractures (LINDGREN)

In all the fracture cases, there was a local clearly delimited area of increased density in the soft tissues near the dorsoradial aspect of the scaphoid bone (Figs 1, 2, 5, 6, 7) The anatomical background underlying this change was studied both by making comparisons with arthrograms of the wrist from adults and by roentgen examination of specimens Judging by ten arthrographic examinations, the joint capsule on the dorsoradial aspect of the scaphoid bone formed a recess corresponding in position to the anatomic snuffbox ('tabatiere anatomique', Fig 3) After injection of 3 ml of water (Fig 4 b) and 2 ml of Urografin 30 % (Fig 4 c), the recess could be well demonstrated



F g 4 F lms obtained in extreme pronat on for demonstration of th joint-capsule recess in a 16-year old boy Normal soft tissue before (a) and after (b) jection of 3 ml v ater into the rad ocarpal joint at the s te f th ulnar stylo d p ocess causing exp ans on of the capsule recess (←) c) The same jo nt filled with 2 ml U ografin 30



Fig 5 A fragment a ulsed at the typ cal sit visibl in pronation only in a 9-year-old girl a) Healthy s d b) R c nt a uls on (←) assoc ated w th effus on nto the joint-capsule recess (←) c) Four v eeks after the accident the a uls on is healed and the effusion has subs ded



Fig 6 a) Avul on of a small fragm nt (←) at the typ cal site vis ble only in extreme pronation, associated with an effus on n the joint-capsule recess (←) b) Healthy s de for comparison.

F g 7 a) and b) Lateral oblique *projections* Supernumerary oss fication centres at the tubercle (←) and ad l stylo d p ocess (os radiale ext ←) c) Typical avuls on of a small fragment visible only in extreme pro at on (←)



Fig 2

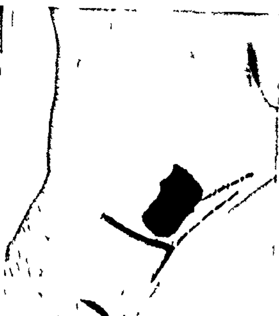


Fig 3

Fig 2 Avulsion of small fragment from distal surface of scaphoid bone in a 14 year old boy The fragment (←) is only visible in the true frontal projection with slight pronation (the upper views) The effusion in the joint capsule recess is best seen in extreme pronation (← in lower left view) The healthy side is shown for comparison (lower right)

Fig 3 Photograph of the pronated hand for demonstration of the relationship of the dorsoradial aspect of the scaphoid bone and the anatomic snuffbox which is bordered by the tendon of M extensor pollicis longus (— — —) and brevis (— — — —)

A shell shaped ossification centre at the tuberosity of the scaphoid (Fig 7), observed in 20 cases in our series, was of interest from the differential diagnostic point of view If its shape and position are taken into consideration there should be little risk of misinterpreting this as a fracture Nor should any differential diagnostic difficulties arise in the interpretation of other, more uncommon, separate ossification centres such as the os centrale, epi and hypo lunatum, radiale externum, and trapezium (KOHLER & ZIMMER, O RAHILLY)

As the small avulsions of flake like fragments from the dorsoradial aspect of the scaphoid bone lay close to the uneven zone on the scaphoid forming the insertion for the capsule in the radio scaphoid and multanguli scaphoid joints (see the schematic drawing to the extreme left in Fig 9), it seems highly probable that they had arisen as a result of chipping at the capsular insertion

Discussion

In BACORN & KURTZKE's review of 2 566 hand lesions in patients over 15 years of age the incidence of scaphoid fractures was 2 7 % Approximately the same incidence was noted in our material consisting exclusively of children

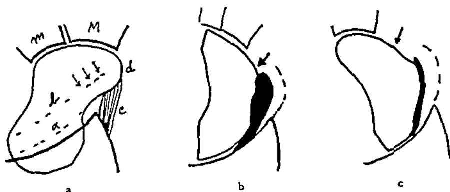


Fig 9 a) Schematic drawing of a dissection of the dorsal aspect of the scaphoid bone placed in the lateral oblique position. The letters *a* and *b* indicate insertion of ligamentary joint capsule facing the radius and the multanguli respectively On extension of the wrist the radius moves towards the line *a* where its action will be arrested by strong ligaments (*c*) connecting the radial styloid process and the tubercle of the scaphoid (*d*) The multanguli bones are arrested at line *b* their motion being halted by the dorsal joint capsule In extreme extension small flakes of bone may become avulsed along the line *b* M — multangulum majus m — multangulum minus b) and c) Schematic drawings of roentgenograms with the hand in slight and extreme pronation respectively The small fragments avulsed from the dorso-radial surface are now projected free from the main bone and become evident The black areas correspond to the normal joint capsule recess which becomes expanded (———) when a fracture of the scaphoid has occurred ↓ points to typical site of avulsion.

It should be stressed that the conventional frontal and lateral projections commonly used in injuries of the distal end of the forearm are equally as important for the detection of scaphoid fractures as the pronation and oblique projections (Fig 2) The prognosis in regard to healing is good Bony union occurred within 7 weeks in the transverse fractures and within 6 weeks in the cases with avulsion Although the latter injuries may be described as trivial, they may cause persistent pain if the wrist is not immobilized for a period of at least two weeks The primary diagnosis of these small lesions may therefore be considered valuable

SUMMARY

One hundred cases of fracture of the carpal scaphoid bone in children have been studied Fifty two of these were avulsions of small fragments from the radial-dorsal aspect of the scaphoid Exudation into the joint-capsule recess of the scaphoid was consistently observed in all fractures of the scaphoid or other carpal bones and this sign may thus be useful as a diagnostic aid in uncertain cases

ZUSAMMENFASSUNG

Es wurden 100 Navikularefrakturen an Kindern studiert In 52 Fallen handelte es sich um kleine Fragmentabrisse vom radialen dorsalen Teil des Kahnbeins Bei allen Frakturen sowie auch bei den Frakturen der übrigen Handwurzelknochen konnte konstant ein Erguss im navicularen Gelenkskapselrecessus festgestellt werden Sein Vorhandensein kann bei fraglichen Fallen von diagnostischer Bedeutung sein

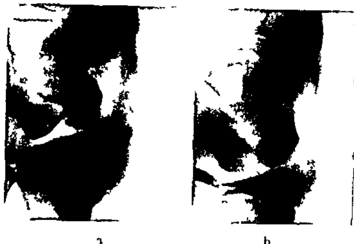


Fig 8 a) Swelling of the external soft tissue in a case of fracture of the metaphysis of the radius No expansion of the joint capsule recess is visible b) Healthy side for comparison

under 15 years of age, scaphoid lesions comprised 2 9 % of this series and were commonest between the ages of 11 and 13 years

Injuries of the scaphoid bone have been said to be more uncommon in children than in adults This view has probably arisen because the fractures are less marked in children and thus are easily overlooked

Waist fractures predominate in adults, in our series these were present in only one sixth of the cases Fractures through the proximal part of the bone were entirely absent in our material As fractures in the distal area usually occur in the child as fissures, the roentgen films must be of high quality Avulsions with detachment of small fragments from the dorsoradial surface of the scaphoid constituted 52 % of our material and thus may be regarded as typical of childhood These fragments are best seen if the wrist joint is placed in more or less extreme pronation so that the fracture surface is taken in a projection tangential to the beam (see the middle and extreme right schematic drawings in Fig 9) This projection has occasionally been used by earlier investigators, but not with a view to studying this type of avulsion or diagnosing the joint capsule effusion As LINDGREN has pointed out, it is important from the technical standpoint that films without intensifying screens should be used This technique gives good delineation of soft tissue changes as well, and consequently permits the demonstration of exudations into the joint capsule recess of the wrist Such exudations occur consistently in fractures of the scaphoid and other carpal bones, but are rare in other injuries of the wrist The exudations have been described clinically as 'swelling of the anatomic snuffbox (Fig 3) and considered typical of fractures of the carpal scaphoid (WATSON JONES)

In accordance with the usual practice in paediatric roentgenology we examined the healthy side as well, the films of the unaffected side were of considerable assistance in the diagnosis of effusion in the joint capsule recess The degree of this swelling in the scaphoid capsule recess was not dependent on the type of the fracture, and with healing of the fracture the effusion subsided (Fig 5)

FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF SOLVE WELIN), MALMO ALLMANNA SJUKHUS MALMO SWEDEN

HAEMODYNAMICS OF THE PELVIC VEINS IN INCOMPETENCE OF THE FEMORAL VEIN

by

GORAN NYLANDER

The strain obstruction syndrome of the femoral vein described by GULLMO (1957) has received much space in the discussion of the aetiology of varices This phenomenon, which occurs in patients with incompetent veins of the legs consists of complete obstruction of the femoral vein distal to the inguinal ligament on straining (Fig 1)

In the GULLMO (1956) modification of the DOS SANTOS and LUKE method for retrograde femoral phlebography, contrast medium is injected percutaneously into the femoral vein just below the inguinal ligament while the patient is straining If the valves in the femoral vein or the long saphenous vein are incompetent the medium will flow in a retrograde direction down through the leg veins If the valves are competent, however the contrast medium will pass down only to the first valve of the respective veins and the remainder will fill the femoral and external iliac veins proximal to the site of injection (see Fig 2) GULLMO (1957) suggested that this phenomenon might be due to a compression of the femoral vein in the lacuna vasorum by a latent femoral hernia bulging down into the femoral canal in association with straining Femoral herniation would according to this author compress the vein and thereby obstruct venous drainage of the leg and favour the development of varices

Submitted for publication 20 April 1961

RÉSUMÉ

L auteur a étudié cent cas de fracture du scaphoide carpien chez l enfant Dans cinquante deux cas il s agissait d arrachement de petits fragments de la face radio dorsale du scaphoide Dans toutes les fractures du scaphoide ou des autres os du carpe on a constaté de façon constante, un épanchement dans le récessus scaphoidien de la capsule articulaire ce signe peut donc contribuer au diagnostic dans les cas douteux

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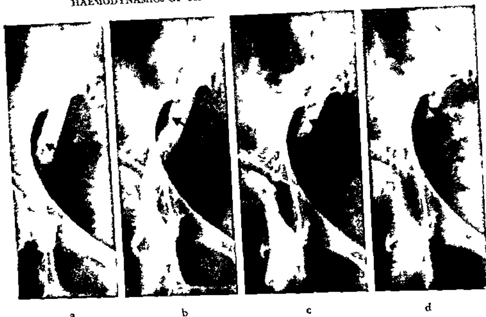


Fig 3 External iliac vein in frontal projection a) Normal width b) Initial phase of straining c) Decreased diameter d) Vein pressed against the psoas muscle

expand to such an extent that the pressure in the vein will equal the intra abdominal pressure Once this stage has been reached the retrograde flow will cease

This theory is supported by observations made in an investigation described below

Personal investigation

In 39 subjects without any signs of incompetence of the femoral vein the width of the vein between the inguinal ligament and its uppermost valve was found to widen on the average from 14 to 17 mm during straining If it be assumed that the lumen of the vein at this level is circular this will imply an increase in the calibre of the vein from 165 to 225 mm² corresponding to 36 % of the transverse area of the vein The increase in the width of the femoral vein in association with straining is illustrated in Fig 2 which also shows that the external iliac vein is well filled both before and during straining and that the width of this vein is not substantially affected

In patients with incompetent veins and the strain obstruction syndrome straining has the opposite effect (Fig 3) To demonstrate this difference a thin polythene catheter was inserted percutaneously into the femoral vein and advanced until its tip lay in the external iliac vein (cf SELDINGER) The



Fig 1 Complete obstruction of the femoral vein on straining





Fig 2 Normal femoral vein without straining (left) and with straining (right)

These theories have, however, not been generally accepted, and the role played by purely mechanical factors in the aetiology of varices is not properly understood

From a haemodynamic point of view a normal vein differs from a vein with incompetent valves in that under certain conditions the blood in the latter can be made to flow in a retrograde direction while in normal veins this is soon prevented by the venous valves In the interpretation of the occlusion phenomenon it is necessary first to realize what happens in a normal vein in the *lacuna vasorum during straining Straining is accompanied by a marked* fairly rapid increase in the intra abdominal pressure (LIEDHOLM 1939, MENCERT & MURPHY 1934) Since the inferior vena cava and the common, external and internal iliac veins lie within the muscle walls responsible for the increase in the intra abdominal pressure during straining, the pressure in the abdominal veins will also be increased to a corresponding degree The intra abdominal pressure during straining considerably exceeds the pressure in the soft tissues in the trigonum femorale and thereby also in the femoral vein, the consequent difference between the pressure in the veins above and below the inguinal ligament causes blood to flow from the external iliac vein to the femoral vein This retrograde flow closes the uppermost valves in the femoral vein and the long saphenous vein Because of the increased pressure the vein distal to the inguinal ligament will be distended from the ligament down to the level of the first valve and the proximal part of the femoral vein will

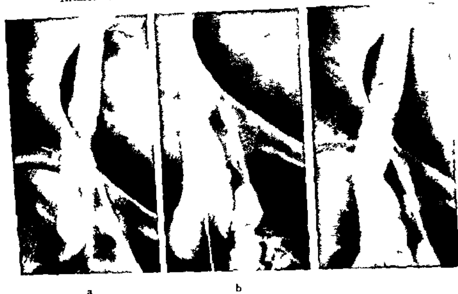


Fig 5 a) Femoral vein without straining b) Occlusion phenomenon during straining c) Elimination of occlusion upon application of cuff around the thigh

iliac vein in the lesser pelvis down to a level below the inguinal ligament, where the increased intra abdominal pressure no longer makes itself felt This compression cannot be due to femoral herniation If it were, the veins would be compressed only at the level of the hernia in the femoral canal

This assumption is also supported by the following observations Thirty seven patients exhibiting the occlusion phenomenon on retrograde femoral phlebography were examined by the following method A cuff was placed around the thigh about 20 cm below the inguinal ligament and inflated to a pressure of about 150 mm Hg The patients were then reexamined under conditions otherwise identical with those which caused the compression of the femoral vein in no instance was the so called occlusion phenomenon observed

The phlebograms reproduced in Fig 5 are from three examinations performed in succession on one and the same patient with the femoral vein without straining (a), the occlusion phenomenon during straining (b) and elimination of the phenomenon on application of a cuff around the thigh (c) This sequence of events is also supported by the investigation of BORGSTROM et coll who found that it is not possible to control the compression phenomenon by femoral hernioplasty by the methods of BURTON or McVAY

It appears that the occlusion phenomenon can occur only if the leg veins are incompetent i e if the flow can be reversed

In Fig 6a a schematic illustration is given of the lacuna vasorum showing

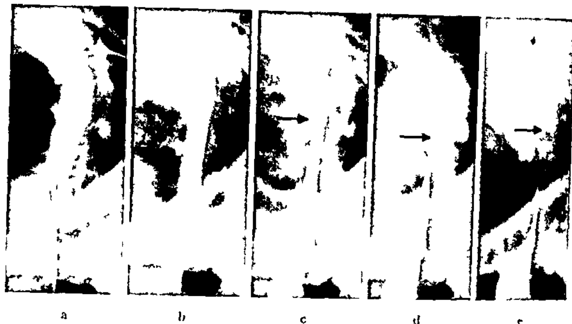


Fig 4 Roentgenograms with beam forming a tangent with the ileo-psoas muscle

catheter was fine and flexible so that it could not influence the occlusion Urografin 60 % was injected continuously throughout the investigation The patient was instructed first to relax and then to strain as much as possible in order to secure roentgenograms of the external iliac vein and femoral vein before and during straining Films were taken at a varying rate of 2 to 4 per second with an automatic film changer

In Fig 3, (a) depicts the normal width of the external iliac vein in the frontal projection with the patient relaxed, while the initial phase of straining with the contrast medium passing down through the external iliac vein towards the femoral vein is illustrated in (b) The diameter of the external iliac vein has begun to decrease in (c) and a small portion of the contrast medium injected through the catheter has passed up to the vena cava, while the bulk of the medium has been forced down in a retrograde direction into the femoral vein In (d) it is shown how the external iliac vein is pressed against the psoas muscle and cannot be filled with medium despite continuous injections This sequence of events was accompanied by the occurrence of a typical occlusion phenomenon below the inguinal ligament

In order to demonstrate the compression of the vein in another plane, the patient was turned through 45° and a film was obtained with the beam forming a tangent with the ileo psoas muscle (Fig 4), the compression and emptying of the external iliac vein was then more distinct What really happens during the so called occlusion phenomenon, is thus not simply a local compression of the vein distal to the inguinal ligament but a compression of the entire external

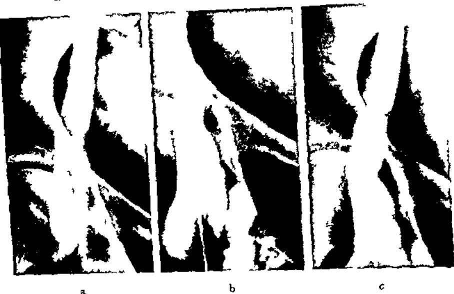


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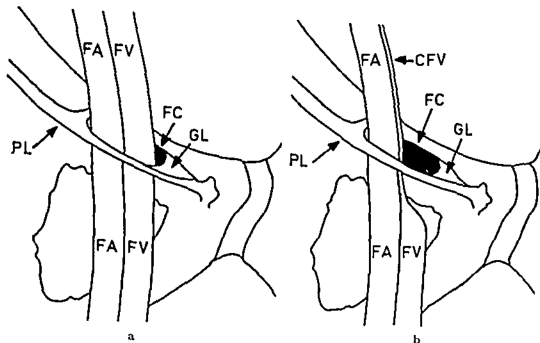


Fig 6 Schematic illustration of lacuna vasorum FA — Arteria femoralis FV — Vena femoralis PL — Ligamentum inguinale GL — Ligamentum Gimbernati FC — Canalis femoralis CFV — Compressed vein

the femoral artery and vein, the lacunae and the perivascular space with the area medial to the latter, between the vein and ligamentum Gimbernati, covered by a thin fibrous septum, Cloquet's septum, which consists of a continuation of the connective tissue sheath of the vessels, fascia transversa and the peritoneum As stated previously, the femoral vein expands and fills the femoral canal during straining This mechanism protects the vulnerable fibrous septum in the femoral canal from being affected by the increased intra abdominal pressure during straining although, in patients with incompetence of the femoral vein and exhibiting the occlusion phenomenon, straining has the opposite effect on the femoral canal

In Fig 6b it is illustrated how the femoral canal increases markedly in width on occlusion of the vein in association with straining The fibrous septum which occludes the femoral canal is now distended to such an extent as to reach from the ligamentum Gimbernati outwards to the medial wall of the artery, against which the vein is compressed

It is generally recognized that the femoral canal is a common site of hernia of the abdominal wall, a locus minoris resistentiae The femoral canal is nevertheless not a preformed but rather an acquired outlet (DICKSON, TASCHE, WILMOTH) There is also a clear correlation between femoral herniation and varices GULLMO (1957) has demonstrated the occlusion phenomenon as such and its relation to venous incompetence, as we have shown, this occlusion

implies severe trauma to a fibrous structure whose function is to close a hernia outlet

When femoral herniation and venous incompetence occur together, there appears to be some justification in a suming that incompetence of the venous valves occurs first and that femoral herniation is a equela, in other words that femoral herniation is due to venous incompetence This point is receiving further attention

SUMMARY

The normal haemodynamics of the external iliac and femoral veins were investigated in 39 subjects and compared to those observed in the p esence of valvular incompetence Straining in normal subjects appears to close a latent hernia outlet whil in the strain obstruction syndrome the outlet is opened If femoral herniation and valvular incompetence occur in the same patient there is reason to assume that the incompetence is *primary and a causal factor* in the former

ZUSAMMENFASSUNG

Die normale Hamodynamik der Vena iliaca externa und *der Vena femoralis* wurde bei 39 Personen untersucht und mit d r Hamodynamik *verglichen welche* beim Vorliegen einer Klappeninsuffizienz beobachtet wird Anspannung bei Normalpersonen scheint *eine latente* Bruchpforte zu verschliessen wahrend beim Spannungsobstruktionssyndrom die *Pforte offen* steht Treten femorale Hernnierung und Klappeninsuffizienz bei einem und demselben Patienten auf ist man zu der Annahme berechtigt dass die Insuffizienz das *Primare ist und* als kausaler Faktor in dem Vorhergenannten wirkt

RÉSUMÉ

L auteur a étudié l hémodynamique normale de la *veine iliaque externe* et de la veine fémorale chez 39 sujets et l a comparée à l hémodynamique *dans les* cas d insuffisance valvulaire Chez les sujets normaux il semble que l *effort ferme un* orifice herniaire latent alors que dans le syndrome d obstruction à l effort l *orifice est ouvert* Si un même malade présente une herni crurale et une insuffisance valvulaire il *y a des* raisons de supposer que l insuffisance valvulaire est primitive et est un facteur causal de la hernie

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FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR ASSOC PROF KURT LIDEN) UNIVERSITY OF LUND SWEDEN

RADIATION BEHIND A GRID DURING ROENTGENOGRAPHY

by

BENGT BJARNGARD and GUNNAR HETTINGER

The radiation behind the patient during roentgenography is composed of photons coming directly from the focus (primary radiation) and photons that have undergone one or more Compton scatterings within the patient (scattered radiation) The purpose of using a grid is to absorb the scattered radiation which merely reduces the diagnostic usefulness of the roentgenogram

The primary radiation transmitted through the patient can be calculated from published roentgen spectra (3) The spectral and angular distribution of the scattered radiation behind slabs of water irradiated by photons with energies between 50 and 250 keV was recently investigated (2) Starting from these spectra one can calculate the filtering effect of a grid However a close analysis of the efficiency of a grid must include a study of the radiation generated in the grid itself This grid radiation is composed of photons Compton scattered mainly in the interspacing material and of characteristic K radiation generated when primary and scattered photons are photoelectrically absorbed in the lamellae

Extensive experimental and theoretical studies have been made of the practical usefulness of different types of grids used in roentgenography (1, 4 5, 6) but no experimental determination of the grid radiation has been carried out

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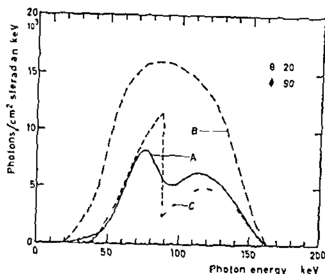


Fig 3 Spectra of radiation in direction θ = 20°, Φ = 90°, when the average primary flux leaving grid is one photon per cm². A Measured spectrum behind grid B Radiation scattered from water phantom C The part of B transmitted through grid according to calculations

tered photons The maximum energy of the primary photons was about 170 keV When Compton scattered 20° or 80°, the resulting photons acquire energies that agree well with the upper energy limits in Fig 2 Most of the once scattered photons have energies above the K-absorption edge of lead (88 keV) Any appreciable contribution from multiply scattered photons to the low energy peak is not probable, since the grid is thin This low energy peak in the spectra has the same shape and height in all scattering angles Θ, while the upper part of the spectrum agrees with the laws of Compton scattering The low energy peak is therefore almost entirely due to lead K radiation which has an average energy of 76 keV

After a graphical integration over all directions Θ, Φ the composition of the grid radiation was estimated to be about 75 per cent lead K radiation and 25 per cent Compton scattered radiation The total spherical number flux of the grid radiation was 0 03 photons per cm², when the primary flux leaving the back of the grid was one photon per cm² averaged over the grid surface (Table, p 382) The fractional number transmissions of the grid to primary photons were 0 00 behind the lead lamellae and 0 93 behind the aluminium Thus the average number transmission of the grid was 0 80

The solid curves (A) in Figs 3 and 4 show spectra of the scattered radiation behind the grid in the directions Θ = 20°, Φ = 90°, and Θ = 80°, Φ = 90°, respectively, when the grid was placed close behind the 15 cm thick water phantom For comparison two more spectra are drawn in each diagram The dashed curves (B) correspond to the scattered radiation leaving the water slab in the direction in question (2) The radiation transmitted by the grid is represented by the curves denoted with a C These spectra are calculated from

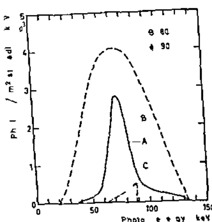


Fig 4 Spectra of radiation in the direct on θ = 80 Φ = 90 when average primary flux lea ing grid is one phantom per cm A Measured spectrum behind the grid B Radiat on scattered from the water phan tom C The part of B that is transmitted th ough the grid accord ng to calculations Difference between measured spectrum (A) and c lculated (C) is due to grid radiat on

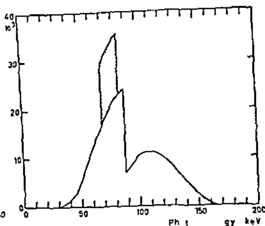


Fig 5 Spectrum of the spherical flux of secondary rad ation behind the grid Th K radiation is represented as a bar and the Compton scattered com ponent of the grid radiation is included in the upper part of the spectrum One primary photon per cm is on an average leaving the surface element observed The average energy of the primary photons is 116 keV

(B) and the attenuation factors used were calculated with regard to the geom etry of the grid

The discontinuity at 88 keV in the calculated spectra (C) is due to the ab sorption edge of lead In the measured pulse height distributions (curves A) this discontinuity is smoothed out In Fig 3 there is a good agreement between the surfaces under the curves (A) and (C) The grid radiation is relatively un important in the direction Θ = 20 , Φ = 90 This is not true in the direction Θ = 80° Φ = 90 (Fig 4) The great difference between the measured and the calculated spectra (A and C, respectively) is caused by the grid radiation generated by the primary radiation and by the radiation scattered from the water phantom

None of the spectra in Figs 3 and 4 was corrected for the resolution Calcula tions have shown that no appreciable error is introduced in the surfaces of the curves when this correction is neglected All the distributions are represented in absolute units

When we integrate over all directions Θ Φ the spherical flux is obtained Fig 5 shows the spectrum of the spherical flux of the calculated transmitted radiation to which the lead radiation was added as a bar with a width of 15 keV The photons Compton scattered from the grid are included in the upper part of the spectrum The number flux (the surface under the curve in Fig 5)

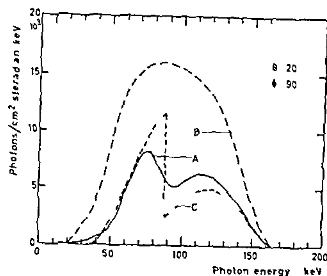


Fig. 3. Spectra of radiation in direction $\Theta = 20°$, $\Phi = 90°$ when the average primary flux leaving grid is one photon per cm². A. Measured spectrum behind grid. *B.* Radiation scattered from water phantom. C. The part of B transmitted *through grid according to calculations.*

tered photons. The *maximum energy of the primary photons* was about *170* keV. When Compton scattered 20° or 80°, the resulting photons acquire energies that agree well with the upper energy limits in Fig. 2. Most of the once scattered photons *have energies above the K-absorption edge of lead (88 keV)*. Any appreciable contribution from multiply scattered photons to the low energy peak is not probable, since the grid is thin. This low energy peak in the spectra has the *same shape and height in all scattering angles* Θ, while the upper part of the spectrum agrees with the laws of Compton scattering. The low energy peak is therefore almost entirely due to lead K radiation, which has an average energy of 76 keV.

After a graphical integration over all directions Θ, Φ the composition of the grid radiation was estimated to be about *75* per cent lead K radiation and 25 per cent Compton scattered radiation. The total spherical number flux of the grid radiation was 0.03 photons per cm², when the primary flux leaving the back of the grid was one photon per cm² *averaged over the grid surface* (Table, p. 382). The fractional number transmissions of the grid to primary photons were 0.00 behind the lead lamellae and 0.93 behind the aluminium. Thus the *average number transmission of the grid* was 0.80.

The solid curves (A) in Figs. 3 and 4 show spectra of the scattered radiation behind the grid in the directions $\Theta = 20°$, $\Phi = 90°$, and $\Theta = 80°$, $\Phi = 90°$, respectively, *when the grid* was placed close behind the 15 cm thick water phantom. For comparison two more spectra are drawn in each diagram. The dashed curves (B) correspond to *the scattered radiation leaving the water* slab in the direction in question (2). The radiation transmitted by the grid is represented by the curves denoted with a C. These spectra are calculated from

from lead is consequently determined by the component with the higher energy, while the build up of photons Compton scattered from the grid was assumed to be energy independent The scattered radiation behind the water slab was calculated from the spectral distributions of reference (2) and then corrected for the attenuation in the grid

The results are included in the bottom line of the table As can be seen the grid reduces the spherical number flux by about a factor of three The grid radiation amounts to about 10 per cent of the total flux of secondary radiation originating from this primary radiation of the diagnostic type It can be expected that the grid radiation is more important when the opening ratio of the grid is decreased and less when the number of electrons per cm^3 of the interspacing material is decreased Though not of the utmost importance it is obvious that the grid radiation cannot be neglected when constructing grids giving an optimum image quality

The errors in the data presented in the table were estimated The values for the number flux of the grid radiation are particularly uncertain Calculations showed that the limits of error were about — 10 and + 50 per cent

Acknowledgements

The authors wish to express their sincere thanks to K Lidén and C Carlsson for their valuable suggestions

SUMMARY

The composition of the radiation behind a diagnostic grid was studied with a scintillation spectrometer The quantity and quality of the secondary radiation generated in the grid was estimated In a practical case the grid radiation amounted to about 10 per cent of the secondary radiation behind the grid

ZUSAMMENFASSUNG

Die Zusammensetzung der Strahlung hinter einem Streustrahlenraster wurde mit einem Szintillationsspektrometer studiert Die Quantität und die Qualität der im Raster erzeugten Streustrahlung wurde beurteilt In einem aktuellen Fall fand man dass die Rasterstrahlung etwa 10 der hinter einem Raster vorkommenden Streustrahlung ausmacht

RÉSUMÉ

Les auteurs ont étudié au moyen d un spectromètre à scintillations la composition du rayonnement derrière une grille de diagnostic Ils ont évalué la quantité et la qualité du rayonnement secondaire engendré par la grille Dans un cas pratique le rayonnement de grille s élève à environ dix pour cent du rayonnement secondaire derrière la grille

Table

Spherical number flux of secondary radiation in photons per cm² when on an average one primary photon per cm² leaves the small surface under observation

Primary radiation	Surface of observation was behind	Number flux of secondary radiation			
		Grid radiation due to		Scattered radiation originating from the water (photons cm²)	Total (photons cm²)
		Lead K radiation (photons cm²)	Compton scattering in the grid (photons cm²)		
(E) r ge = 116 keV	Grid alone	0 02	0 01	—	0 03
(E) er g = 116 keV	15 cm water	—	—	3 00	3 00
(F) r ge = 116 keV	Grid behind 15 cm water	0 19	0 06	1 10	1 35
170 kV radiation HVL = 0 4 mm Cu	15 cm water	—	—	3 00	3 00
170 kV radiation HVL = 0 4 mm Cu	Grid behind 15 cm water	0 06	0 06	1 02	1 14

is 1 35 photons per cm² when on the average one primary photon per cm² is leaving the small surface under observation About 20 % of these 1 35 photons is due to grid radiation, mainly as K radiation from lead (see table, above) Without the grid the number flux in the centre of the back of the water slab would have been 3 0 photons per cm² per unit primary flux (2) Thus the grid has reduced the build up considerably by absorbing some of the photons scattered from the water However, this reduction in the number of secondary photons has been counteracted to some extent by the grid itself, when generating its grid radiation as seen in the table

If the energy of the primary radiation is decreased, it can be expected that the contribution from grid radiation decreases The K-radiation component disappears when the photon energy is below the K absorption edge On the other hand, it is probable that the number flux of photons Compton scattered from the grid is approximately independent of the photon energy Other experiments have verified this behaviour for photons scattered from water slabs (2)

As an application of the results of this experiment, we calculated the grid radiation when the water phantom and the grid were irradiated by a roentgen apparatus with 170 kV constant potential and a total filtration of 4 mm aluminium The spectrum of this primary radiation was taken from reference (3) The primary spectrum was divided into two parts, one of which was identical to the spectrum of the primary radiation used in this experiment The other component had very few photons with energies above 88 keV The K radiation

FROM THE GYNECOLOGIC DEPARTMENT (DIRECTOR G GORTON) OF THE KONUNG GUSTAF V JUBILEUMSKLINIK LUND SWEDEN

MALIGNANT NEOPLASMS OF THE VULVA

by

JOHN ERIK JOHNSSON

Malignant tumours of the vulva are relatively rare and are believed to represent only 2 to 10 % of all growths of the female genital tract they occur mainly in elderly women between the ages of 60 and 70 years The results of treatment have not been found to be very encouraging though the primary seat of such tumours as well as the regional lymph nodes are readily accessible to radical surgery

Material The present material consists of 175 cases admitted to hospital during the period 1947—1959 for neoplasms of the vulva These represented 4 2 % of all cases of cancer of the female genital tract admitted during those years The age distribution in the material was as follows 9 patients were between 31—40 years of age (5 2 %), 17 between 41—50 years (9 8 %) 24 between 51—60 years (13 7 %) 52 between 61—70 years (29 7 %), 50 between 71—80 years (28 6 %) 22 between 81—90 years (12 5 %) and one patient finally 91 years of age (0 5 %), thus 71 % of the patients were over 60 and 41 % over 70 years of age

It is usually itching a sore or the detection of a small nodule in the vulva that causes the patient to seek advice Sometimes though rarely the condition is ushered in by bleeding vaginal discharge or difficulty in micturition, it should however be observed that the initial symptom in growths of the clitoris is often a sensation of burning on micturition Eighty one per cent of the patients

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FROM THE GYNECOLOGIC DEPARTMENT (DIRECTOR G GORTON) OF THE KONUNG GUSTAF V JUBILEUMSKLINIK LUND SWEDEN

MALIGNANT NEOPLASMS OF THE VULVA

by

JOHN ERIK JOHNSSON

Malignant tumours of the vulva are relatively rare and are believed to represent only 2 to 10 % of all growths of the female genital tract, they occur mainly in elderly women between the ages of 60 and 70 years The results of treatment have not been found to be very encouraging though the primary seat of such tumours as well as the regional lymph nodes are readily accessible to radical surgery

Material The present material consists of 175 cases admitted to hospital during the period 1947—1959 for neoplasms of the vulva These represented 4 2 % of all cases of cancer of the female genital tract admitted during those years The age distribution in the material was as follows 9 patients were between 31—40 years of age (5 2 %) 17 between 41—50 years (9 8 %) 24 between 51—60 years (13 7 %) 52 between 61—70 years (29 7 %), 50 between 71—80 years (28 6 %) 22 between 81—90 years (12 5 %) and one patient finally 91 years of age (0 5 %) thus 71 % of the patients were over 60 and 41 % over 70 years of age

It is usually itching a sore or the detection of a small nodule in the vulva that causes the patient to seek advice *Sometimes* though rarely, the condition is ushered in by bleeding vaginal discharge or difficulty in micturition it should however be observed that the *initial* symptom in growths of the clitoris is often a sensation of burning on micturition Eighty one per cent of the patients

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had reported a sore, and/or nodule and/or pruritus as the first symptom, pain also occurred in advanced cases Pruritus, which is one of the predominant symptoms, is also a cardinal symptom of other conditions of the vulva such as kraurosis and leukoplakia, the number of cases in which kraurosis and leukoplakia precede or accompany the appearance of cancer of the vulva varies widely from one series to another (13 to 75 %, SCHOMIG et coll 1950, MOBIUS 1951) probably because the skin changes are not always noted In the present material such cutaneous changes were present in 33 % of the cases

The tumours usually arise in the labium majus or labium minus, less frequently in the clitoris or posterior commissure The tumour was situated in the labium majus or labium minus in 138 cases, in the clitoris in 28, and in the posterior commissure in 9 cases Tumours of the vulva are classified into groups and stages according to their appearance, local spread, and the presence or absence of clinical metastases This classification is not uniform and varies from one hospital to another and from examiner to examiner BERVEN (1941) classified tumours of the vulva as follows

Group I Non ulcerated tumour localized to the (a) labium majus and minus, (b) clitoris, (c) posterior commissure,

Group II Ulcerated tumour of same spread as in group I,

Group III Tumour involving more than one of the three above mentioned sites,

Group IV Tumour infiltrating contiguous tissue (vagina, perineum, urethra, genito femoral fossa)

Stage I Without clinical metastases in inguinal lymph nodes,

Stage II Probable involvement of still movable inguinal lymph nodes,

Stage III Probable involvement of inguinal lymph nodes fixed to contiguous tissue

Most of the malignant vulvar tumours are of the squamous cell variety (80 to 90 %), the remainder consisting of adenocarcinomas, basal cell carcinomas, malignant melanomas and malignant hydradenomas The present material comprised 158 cases of squamous cell carcinoma, 10 of malignant melanoma, 4 of basal cell carcinoma, 1 of adenocarcinoma, 1 of low differentiated carcinoma and 1 case of sarcoma The tumours grow fairly rapidly in the loose subcutaneous tissue of the vulva and soon spread to the local lymph nodes Forty five per cent of the patients had had symptoms for six months or less, and 34 % for more than one year About half of all the patients had metastases in one or both groins on admission (Tables 1 and 2)

Table 1

Case material (1947—1959) grouped according to local extent of involvement

	Number of patients	Number of patients operated upon
Group I	39 (22 3 %)	38
Group II	87 (49 6 %)	84
Group III	45 (25 8 %)	41
Group IV	4 (2 3 %)	3
Total	175	166 (95 %)

Table 2

Case material grouped in stages according to absence or presence of metastases 1947—1959

	Number of patients	Number of patients operated upon
Stage I	95 (54 5 %)	94
Stage II	52 (29 6 %)	52
Stage III	28 (15 9 %)	20
Total	175	166 (95 %)

Treatment and Results

In many hospitals treatment is still only by surgical operation with more or less radical extirpation of the tumour as well as of the inguinal lymph nodes on one or both sides sometimes with removal of the pelvic lymph nodes The results have not proved encouraging Five year cure rates of 30 to 45 % have been reported but the figures are usually lower (TAUSSIG 1940 KOTEK 1949 ISTRE 1951 CASSIDY 1957)

The survival rate of patients who received radiotherapy only was originally even lower (11 to 12 %) though it was later improved (26 %) by the use of special techniques Recurrences appear to be more common (KOTEK 1949 TODD 1949 ELLIS 1949 MOBIUS 1951 HUBER 1953) Combined surgical and radiation therapy has also not given a 5 year cure rate of more than 25 to 38 % (BERVEN KOTEK)

The results obtained in two recent series are however more promising Thus STENNING & ELLIOT (1959) reported a 5 year cure rate of 60 % in patients with vulvar carcinoma of the squamous cell variety only and WAY (1960) gave a corresponding rate of 61 % and 49 % in two series of 79 and 96 cases respectively Treatment consisted of radical excision of the vulva and bilateral removal of the regional (inguinal and pelvic) lymph nodes



a b c

Cancer of the vulva (a) at ten days after electrocoagulation (b) and when the vulva had healed (c)

Combined surgical and radiation therapy has been our rule since 1947 The surgical part of the treatment consists of radical electrocoagulation of the entire vulva as described by BERVEN In cases in stage I (no clinical metastases in inguinal lymph nodes) the surgical treatment is limited to this procedure A moderate dose of telegamma or roentgen rays is given to the inguinal lymph nodes In stages II and III (with involvement of the lymph nodes) treatment is extended *to include irradiation and subsequent removal of the inguinal lymph* nodes on the side(s) involved If operation reveals gross signs of involvement of the pelvic lymph nodes, they are also removed

Of the 175 patients 5 were very old and in a poor general condition and had advanced tumours, 3 of these received no treatment and 2 palliative treatment only Four others had been operated upon elsewhere and had been referred to the department for postoperative irradiation of the inguinal lymph nodes The remaining 166 cases (95 %) were treated in the way outlined above Electrocoagulation *of the vulva was performed in all of the cases except two* The postoperative complications were few Two patients died within 2 weeks of operation (pulmonary embolism and cerebral haemorrhage) In one patient bleeding from the wound was so profuse as to cause a fall in blood pressure In 9 cases (5 5 %) the body temperature was at least 39° C for more than 48

hours after the operation In 7 cases radical removal of the tumour required extirpation of the anal region with the sphincter and the lower part of the rectum after transversostomy One patient died from peritonitis complicating colostomy prior to planned radical electrocoagulation

Twenty three (14 %) of the cases treated with electrocoagulation had local recurrences In one case bilateral ureterosigmoidostomy was done because of severe urethral stricture Moderate stricture of the urethra developed in one case In another case the pudendal nerve was divided on both sides because of persistent intense pruritus after the vulva had healed and in still another case division of the nerve was also considered but was postponed because the itching abated The operation was followed by stenosis of the introitus of the vagina in 7 and by prolapse in 4 cases

In 73 (41 5 %) of the cases the inguinal lymph nodes were excised and in 27 the pelvic lymph nodes also were excised In 2 of them the vulvar tumour had been radically excised at another hospital For such a major operation on these relatively old patients the frequency of complications was low The operative mortality (within 2 weeks of operation) consisted of one death from acute heart failure on induction of anaesthesia and in four cases the post operative course was complicated by bleeding from the wound

Excision of the inguinal and/or pelvic lymph nodes was followed by ipsilateral or bilateral leg oedema in 46 5 % of cases Such swelling did not appear to be more common among those with microscopically verified involvement of the lymph nodes but the series was not large enough to permit any valid conclusions The symptoms after operation were slight or insignificant except in those cases in which the growth had invaded the perinodular fatty tissue when they were severe In 2 cases inguinal hernia occurred after the operation

All of the 10 cases of malignant melanoma were treated with electrocoagulation and in 6 of them treatment was extended to include excision of the lymph nodes Two of these cases are now symptom free six years and six months respectively after the operation One has survived two and a half years but has symptoms of remote metastases The remaining 7 patient died from remote metastases (lungs skeleton liver) two months to one year after the operation The two patients with sarcoma and low differentiated carcinoma respectively have died from their diseases The four patients with basal cell carcinoma are still alive with no signs of recurrence in one of them a local recurrence however developed but the patient is now symptom free (follow up 5 years)

The 5 year cure rate may be assessed on the basis of 102 cases (93 of squamous cell carcinoma 6 of malignant melanoma 2 of basal cell carcinoma and 1 case of sarcoma) treated in 1947—1954 Of these 97 cases (95 %) were treated in the way described above and 52 patients (51 %) are still alive and symptom free more than 5 years after the operation Of these 52 patients however 4 have had local recurrences 5 years after the first operation These recurrences have been treated with electrocoagulation

Table 3

Cases grouped in stages according to absence or presence of metastases during the period 1947—1954

	Number of patients	Number of patients operated upon	Symptom free for at least 5 years
Stage I	48 (47 %)	47	29 (60 %)
Stage II	36 (35.3 %)	35	17 } (42.5 %)
Stage III	18 (17.7 %)	15	6 }
Total	102	97 (95 %)	52 (51 %)

As expected, the prognosis of stage I, i. e. patients without clinical involvement of the local lymph nodes, is much better than that of stages II and III. As known, palpation cannot always indicate whether a lymph node is involved or not. According to BERVEN, about 20 % of patients are erroneously classified as stage I. If this were so in the present series, it would mean that by no means all the lymph nodes involved were excised. An attempt was therefore made to clarify this point and decide whether it might be of prognostic significance.

During the period 1947—1954 a total of 48 cases were classified as stage I. Of these, involvement of the lymph nodes was later diagnosed in eleven. Microscopic examination showed evidence of cancer in all of them. The follow up in all these cases is still less than 5 years. In 9 cases the tumour continued to grow in the perinodular fatty tissue.

In the entire material (1947—1959) a total of 95 cases were classified as stage I. In 23 of these (24 %), metastases to the lymph nodes were diagnosed later and verified histologically. Two other patients also have metastases, but the condition of these is such that operation is not being considered.

Discussion

A series of 175 cases of malignant vulvar neoplasms treated during the period 1947—1959 was analysed. The age distribution, the site, and the microscopic appearance of the tumours were largely the same as in other series. It would appear from the Anglo American literature that there is an increasing tendency to treat the disease surgically with radical removal of the tumour and, unless contra indicated by the patient's general condition, excision of the local lymph nodes, preferably as a single stage operation. With this method a 5 year cure rate of about 60 % has been reported in a few series. The patients in the present material had been treated in this way with radical coagulation of the vulva in 95 % and excision of the local lymph nodes in 41.5 % of the 175 cases. In addition the sites of the lymph nodes were treated radiologically. Of 102 patients (1947—1954), 51 % were still alive and symptom free after 5 years.

The investigation also showed the extremely poor prognosis of malignant melanoma compared with that of basal cell carcinoma despite occasional local recurrences of the latter.

Metastases occurred in local lymph nodes in about a quarter of the cases in which no such involvement could be detected before operation These metastases appeared fairly soon after operation and excision was then difficult In addition most of these cases were not symptom free after the operation The follow up in all these cases is still less than 5 years Since excision of the lymph nodes carries such a very low mortality it would appear wise to extend treatment to include bilateral excision of the local lymph nodes as a routine measure in all cases in which this is possible and not contra indicated by the general condition

SUMMARY

A series of 175 cases of malignant vulvar neoplasms 95 % of which had been treated with radical electrocoagulation of the vulva was analysed The local lymph nodes had been excised in 41 5 % of the cases In addition the sites of the lymph nodes had been treated radiologically A 5 year cure rate of 51 % is reported

ZUSAMMENFASSUNG

Ein Material von 175 Fallen mit malignen Vulvatumoren wurde analysiert von denen 95 mit radikaler Elektrokoagulation der Vulva behandelt worden waren Die lokalen Lymphdrusen waren in 41 5 % der Falle exzidiert Das Lymphdrusengebiet war zusatzlich radiologisch behandelt worden Eine 5 Jahres Heilung von 51 wird berichtet

RÉSUMÉ

L auteur a étudié une série de 175 cas de cancer de la vulve dont 95 % avaient été traités par électrocoagulation radicale de la vulve Les ganglions lymphatiques locaux avaient été enlevés dans 41 5 % des cas De plus l emplacement des ganglions lymphatiques avait été traité par radiothérapie Un taux de guérison de 5 ans de 51 % a été obtenu

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FROM THE DEPARTMENTS OF CELL RESEARCH AND BIOPHYSICS (DIRECTOR PROF SUBODH MITRA) CHITTARANJAN NATIONAL CANCER CENTRE, CALCUTTA INDIA

RADIOPROTECTIVE EFFICACY OF CYSTEAMINE WITH THE MITOTIC INDEX OF RAT BONE MARROW CELLS AS REFERENCE SYSTEM

by

P DE A BOSE and S BOSE

The present work is concerned with the protective efficacy of a given dose (150 mg/kg bodyweight) of cysteamine against a lethal dose (800r) of irradiation during a period of from zero hours to 30 days after irradiation with the mitotic index of rat bone marrow cells as a common biologic reference system The radioprotective efficacy of cysteamine (β mercaptoethylamine) in varying doses has been previously assessed in different species of animals at different intervals after irradiation also in varying doses (BACQ et coll 1953 GROS et coll 1953 GEREBTZOFF et coll 1954 DEVIK et coll 1955 MAISIN et coll 1955 ARMELLINI et coll 1958 FUMAGALLI et coll 1958 CHATTERJEE et coll 1959 and RAY CHAUDHURI 1961)

Material and Method The irradiation tissue collection, fixation, histologic preparations and scoring of data were performed as reported previously (DE et coll 1960) The protective agent cysteamine 150 mg/kg bodyweight was administered intraperitoneally to protected groups of animals immediately before irradiation

A total of 240 rats formed the material in this set of experiments In the early investigation as described in Table 1 (from 5 minutes to 24 hours after irradiation) 135 rats were divided equally into three groups and from each group 3

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Table 1

Correlation of the radioprotective efficacy of 150 mg/kg cysteamine with the mitotic index of rat bone marrow cells irradiated with 800 r

Time interval	Mitotic index %			1st protective index $\left(\frac{P-R}{N-R} \times 100\right)$	2nd protective index $\left(\frac{P}{N} \times 100\right)$	Value of t between (N and P)	Significance at
	Normal control (N)	Irradiated control (R)	Protected series (P)				
5 min	1 39 ± 085	0 92 ± 106	1 07 ± 110	31 %	77 %	9 1	5 % & 1 %
1/4 hr	1 41 ± 096	0 17 ± 084	0 24 ± 071	6 %	17 %	39 0	»
1st hr	1 39 ± 095	0 20 ± 016	0 22 ± 070	2 %	16 %	39 1	»
2nd hr	1 39 ± 100	0 21 ± 080	0 23 ± 096	2 %	17 %	33 1	»
3rd hr	1 40 ± 107	0 22 ± 075	0 24 ± 071	2 %	17 %	36 2	»
4th hr	1 42 ± 078	0 26 ± 074	0 27 ± 088	1 %	19 %	38 3	»
5th hr	1 39 ± 097	0 30 ± 096	0 32 ± 099	2 %	23 %	30 5	»
6th hr	1 41 ± 095	0 26 ± 066	0 37 ± 089	10 %	26 %	31 5	»
7th hr	1 42 ± 103	0 20 ± 060	0 38 ± 084	15 %	27 %	30 5	»
8th hr	1 40 ± 077	0 21 ± 066	0 43 ± 063	18 %	31 %	37 3	»
9th hr	1 39 ± 094	0 23 ± 082	0 44 ± 075	18 %	32 %	30 6	»
12th hr	1 40 ± 085	0 72 ± 084	0 84 ± 080	17 %	60 %	19 3	»
15th hr	1 41 ± 087	0 67 ± 093	0 77 ± 096	14 %	55 %	19 4	»
18th hr	1 39 ± 089	0 43 ± 060	0 72 ± 096	30 %	52 %	20 3	»
21st hr	1 40 ± 100	0 34 ± 095	0 68 ± 054	32 %	49 %	24 8	»
24th hr	1 38 ± 093	0 27 ± 089	0 65 ± 092	34 %	47	22 1	»

rats were assessed in each period In the periods of late investigation (1st day to 30th day after irradiation), 90 rats were selected and arranged in three groups, with an equal number of rats in each group The assessment, as described in Table 2, was performed in 3 rats from each group for each period Unprotected irradiated rats did not survive beyond 12 days

Table 2

Correlation of the radioprotective efficacy of 150 mg/kg cysteamine with the mitotic index of rat bone marrow cells irradiated with 800 r

Time interval	Mitotic index			1st protective index $\left(\frac{P-R}{N-R} \times 100\right)$	2nd protective index $\left(\frac{P}{N} \times 100\right)$	Value of t between (N and P)	Significance at
	Normal control (N)	Irradiated control (R)	Protected series (P)				
1st day	1 38 ± 093	0 27 ± 089	0 65 ± 092	34 %	47 %	22 1	5 % & 1 %
3rd day	1 40 ± 094	0 32 ± 090	0 79 ± 096	44 %	56 %	17 9	»
6th day	1 39 ± 080	0 36 ± 089	0 92 ± 093	54	66	15 1	»
10th day	1 39 ± 062	0 52 ± 093	0 63 ± 060	13 %	45 %	33 0	»
12th day	1 41 ± 092	2 02 ± 124	0 82 ± 084		58 %	19 0	»
15th day	1 42 ± 096	Dead	1 21 ± 075		85 %	6 1	»
18th day	1 40 ± 100	»	1 21 ± 080		86 %	5 9	»
24th day	1 40 ± 097	»	1 29 ± 094		92 %	3 23	»
30th day	1 42 ± 094	»	1 27 ± 099		89	4 28	»

Results

The recording of data proved to be difficult due to death of all the unprotected irradiated animals within twelve days following irradiation The protective index has previously been indicated by the formula

$$\frac{P - R}{N - R} \times 100$$

where N is the mitotic index of bone marrow cells of a normal series R that of an irradiated (unprotected) series and P that of an irradiated but protected series The formula showed the protection as a percentage of the total damage In absence of R after a certain period in the present series another criterion showing the mitotic index in protected animals as a percentage mitotic index in normal animals $\left(\frac{P}{N} \times 100\right)$ was taken into consideration This naturally cannot be regarded as an index of protection but will certainly throw some light on

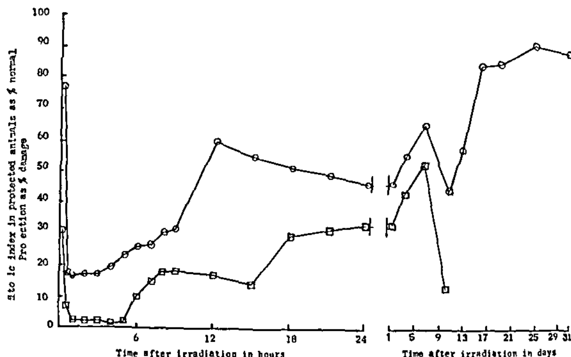


Diagram showing the assessment of the radioprotective efficacy of 150 mg dose of cysteamine per kg bodyweight from 5 minutes to 30 days after 800r irradiation with the mitotic index as the reference system The maximum stable protection (85 to 92 per cent) was reached between the 15th and 30th days

Mitotic index in protected animals shown as % normal $\left(\frac{P}{N} \times 100\right)$

□ Protection shown as % damage $\left(\frac{P-R}{N-R} \times 100\right)$

the process of recovery in protected animals Both these indices are included in the diagram above The data of the period from 5 minutes to 24 hours after irradiation with the first and second indices have been included in Table 1 and the period from 1 day to 30 days following irradiation in Table 2

Discussion

The reference system employed represents the growth manifestations of haemopoietic cells These cells are also highly radiosensitive (Bloom 1948)

The mitotic indices of the protected animals varied from 85 to 92 per cent of that of the normal controls between the 15th and the 30th day after irradiation The protected animals appeared to have fully recovered from the effects of radiation by the 15th day Maximum radiation damage was observed during the 10—12 days period as all the unprotected irradiated animals had died by this time

Ray Chaudhuri reported that cysteamine affords definite, though partial, protection against radiation induced (120r) chromosomal damage in the grass

hopper BACQ et coll studied the radioprotective efficacy of cysteamine (3 mg/animal) in mice with whole body radiation doses of 700r and 900r employing different biologic reference systems (survival index, peripheral leukocyte count bodyweight) The results obtained in the present study are in agreement with BACQ s results Partial protection was observed in this laboratory in the assessment of the protective efficacy of sodium cyanide (1 5 mg/kg and 3 mg/kg bodyweight) against 800r on rat bone marrow cells More perfect protection was afforded on the same biologic reference system against the same radiation dose in the present investigation with cysteamine

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We wish to express our deepest thanks to Prof S Mitra for his support and interest in this investigation Thanks are also due to Mr R Chatterjee Mr K Bhattacharya Dr S K Brahma and Dr S Mondal for their suggestions and active cooperation

SUMMARY

The protective efficacy of cysteamine (150 mg/kg bodyweight) was tested on rat bone marrow cells in vivo with the mitotic index as the biologic reference system during a *period from* 5 minutes to 30 days after 800r irradiation Maximum stable protective efficacy (85 to 92 % *of* that of the normal controls) was observed between the 15th and 30th days

ZUSAMMENFASSUNG

Die strahlenschutzende Wirkung von Cysteamin (150 mgm/Kg Korpergewicht) wurde an Knochenmarkzellen *von* Ratten *in vivo* mit dem mitotischen Index als biologisches Referenzsystem wahrend eines Zeitraumes von 5 *Minuten bis 30* Tage nach Bestrahlung mit 800r untersucht Maximale dauerhafte Schutzwirkung (85 bis 92 der normalen Kontrollen) wurde zwischen dem 15 und 30 Tag *nach der* Strahlung beobachtet.

RÉSUMÉ

Les auteurs ont testé in vivo l efficacité radio*protectrice de la* cysteamine sur des cellules de moelle osseuse de rats Ils ont utilisé comme système de reference biologique l indice mitotique sur une période allant de 5 minutes à 30 *jours* après une irradiation de 800r L efficacité protectrice stable maximale (85 à 92 de celle des témoins normaux) a été observée *entre* les quinzième et trentième jours

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BOOK REVIEWS

VELOPHARYNGEAL FUNCTION IN CONNECTED SPEECH STUDIES USING TOMOGRAPHY AND CINE RADIOGRAPHY SYNCHRONIZED WITH SPEECH SPECTROGRAPHY By Lars Björk 94 pages 42 illus trations and 13 tables Acta radiol (1961) Suppl No 20? Price Sw Kr 25

Methods have been d veloped for high speed cineradiographic studies of the speech organs during connected speech using a roentgen image amplifier a 35 mm film camera and a high fidelity tape recorder for the sound The speech has been analysed according to the visible speech method by means of a special 48 channel sound spectrometer constructed by H Sund It is possible to obtain visible recordings of any length of speech desired A special device syn chronizes each frame of the roentgen cinefilm with the sound

For acoustic calculations of nasality it is of great importance to have accurate information regarding the cross sectional area of the coupling between the nasal and oral cavities this area can be reproduced with relative accuracy during the articulation of single sustained sounds by means of transversal tomography The cross sectional area was found to be mainly elliptical and to be a linear function of its sagittal major axis the length of the latter can be obtained not only from a transversal tomogram but also from a lateral roentgen film of the velopha ryngeal region It is possible in this way to follow the variations in size of the coupling area between the nasal and oral cavities during connected speech

Cineradiographic and sound spectrographic studies of the movements of the soft palate while four test sentences were being read were performed in adult men and women and in children aged 6—8 years The soft palate largely followed a fairly constant pattern of move ments during the pronunciation of these sentences

In normal speech the mean duration of the velum movements from the closed to open state are of the order of 130 msec and the opposite transition i e closure occupies about 160 msec The speed of the velum movements does not change proportionally to the overall speaking rate but tends to be less variable In low normal and high speaking rates corresponding to overall durations of 100—200—300 respectively on a relative scale the velum movements were found to vary in the proportions 100—130—160 The assimilated nasality on both sides of a nasal consonant in connected speech affects a larger part of the speech before the nasal con sonant than after the nasal consonant Even unvoiced stops and fricatives may be affected to some extent without serious effects on speech quality as judged by trained listeners The effect of slight nasalization as in normal speech in segments close to nasal consonants is primarily the reduction of the first formant level against other formants The typical velopharyngeal coupl ing area is of the order of 60 mm^2 The effect of an extremely large degree of nasalization in which the velum may approach the back of the tongue and the velopharyngeal coupling area is of the order of 250 mm^2 is a lowering of the frequency of the first formant (nasal resonance) and a relative decrease of the levels of the second and the third formants Further closure of the nostrils causes an increase in the level of the first formant (low frequency resonance)

The results mentioned may be considered examples of the utility of the method for contin uous studies of the physiologic changes in the speech organs in relation to the connected speech produced The synchronizing device may of course also be used for synchronizing recordings of ECG blood pressure etc with high speed roentgen cinefilms

Autoreview

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BOOK REVIEWS

VELOPHARYNGEAL FUNCTION IN CONNECTED SPEECH STUDIES USING TOMOGRAPHY AND CINE RADIOGRAPHY SYNCHRONIZED WITH SPEECH SPECTROGRAPHY By Lars Bjork 94 pages 42 illustrations and 13 tables Acta radiol (1961) Suppl No 202 Price Sw Kr 25

Methods have been developed for high speed cineradiographic studies of the speech organs during connected speech using a roentgen image amplifier a 35 mm film camera and a high fidelity tape recorder for the sound The speech has been analysed according to the visible speech method by means of a special 48-channel sound spectrometer constructed by H Sund It is possible to obtain visible recordings of any length of speech desired A special device synchronizes each frame of the roentgen cinefilm with the sound

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Autoreview

Das Carcinoma Colli Uteri Seine Prognose und Behandlung mit besonderer Berücksichtigung der Strahlentherapie Von Wilhelmine Janisch Raskovic 619 Seiten 76 Abbildungen und 69 Tabellen Georg Thieme Leipzig 1961 DM 75

This comprehensive monograph is based on a study of 2 701 cases of cervical carcinoma treated from 1927 to 1948 Around a core of abundant information derived from a painstaking analysis of the hospital records of these cases the author presents a broad survey of the changing concepts and approaches to the therapy of cervical carcinoma in this century The author takes as her starting point the contributions of Wertheim to the surgical treatment of this disease The introduction and refinement of radiotherapy of cervical carcinoma are discussed in detail An account is also given of the renaissance of the surgical approach in several European and American centres including the ultraradical technique of Brunschwig and others

The Chemnitz Gynaecologic Clinic where the investigation was carried out is an institution devoted to the radiotherapeutic treatment of carcinoma of the cervix A certain number of cases to be exact 9 2 per cent have however been subjected to surgery mostly combined with radiotherapy The operations were in most cases performed according to Wertheim No hard and fast indications for surgery are laid down but there seems to be a tendency in this clinic to operate upon very early cases of squamous cell carcinoma, adenocarcinoma of the cervix and cervical carcinoma associated with pregnancy

Most of the cases were treated with radiotherapy The technique adopted is a slight modification of the Stockholm method with fractionated radium treatment and roentgen therapy Considerable attention is devoted to the question of the treatment of cervical carcinoma stage 0 which at the author s clinic is treated in the same manner as invasive carcinoma

The results of the various treatments are presented in considerable detail Indications and contra indications complications of treatment routes and frequency of metastases as well as survival rates and the way in which they are influenced by various factors are discussed in detail It is no exaggeration to say that the penetration and analysis of the case material are exemplary

One of the chief merits of the book lies in the discussion based upon detailed studies of the literature which the author gives to her own case material Every aspect of the pathology, clinical picture and therapy of cervical carcinoma is surveyed with impressive knowledge and considerable erudition Thus the various phases in the development of the surgical therapy of carcinoma of the cervix are considered in detail together with the pros and cons of vaginal and abdominal methods There is also a broad description of the main principles of the various important radiotherapeutic centres (Paris Stockholm, Heidelberg München and Manchester) Complications arising in connection with the surgical and radiotherapeutic treatment are closely analysed and related to important etiologic factors Different opinions on the treatment of cervical carcinoma in physiologic (pregnancy) and pathologic conditions are reported

In this comprehensive book in which for example even such relatively border questions as anaesthesia prophylaxis and therapy in cases of thrombosis and embolism are discussed at length the reviewer was however, rather disappointed not to find at least a short chapter on the diagnosis of cervical carcinoma especially with reference to the methods of colposcopy and cytodiagnosis now generally applied It is also surprising that the author completely omits the Grahams investigations of the radiation response even if this method of examination has not been incorporated into the diagnostic arsenal at the Chemnitz clinic

The work would have gained appreciably if the typography had been less cramped and unfortunately the list of errata given in the book might be considerably extended

Sam Brody

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THE SPHENOIDAL SINUS

An anatomical and roentgenologic study with reference to transsphenoid hypophysectomy

by

G HAMMER and C RADBERG

The treatment of tumours of the hypophysis has for long been surgical and during the last ten years hypophysectomy has been introduced as a method of dealing with metastases from carcinoma of the breast and for diabetes mellitus associated with angiopathy (LUFT OLIVECRONA and SJOGREN 1952 1953) The operation is performed by the transcranial exposure of the hypophysis Various types of transsphenoid operations have come into use on an increasing scale ESCHER and ROTH (1957) and GISSELSSON (1957) have employed the transethmosphenoid route by the Chiari method while HAMBERGER et coll (1961) have introduced the transantrosphenoid method

There are numerous anatomical variations of the sphenoidal sinus Variations in its size will affect the boundaries of the hypophysis i e the anterior wall and the floor of the sella turcica will possess a varying thickness and degree of protrusion into the sphenoidal sinus The lateral extensions of the anterior wall and thus the distance between the carotid arteries and the cavernous sinus may vary within a fairly wide range Bony septa frequently occur in the sphenoidal sinus their position is inconstant and they may sometimes impede the surgical approach

The topographic anatomy has a decisive bearing on the operability and surgical approach Preoperative roentgenologic analysis therefore plays an

From the Department of Otolaryngology (Director Prof C A. Hamberger) and Roentgen Department II (Director Docent I Wickbom) Sahlgrenska Sjukhuset Gothenburg Sweden
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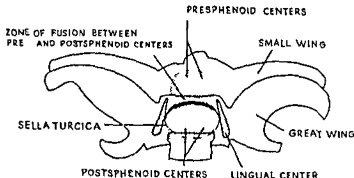


Fig 1 Line drawing of sphenoid bone from above showing the nuclei from which the central parts develop

essential part in planning transsphenoid hypophysectomy and enhances the possibilities for rapid and uncomplicated conduct of the operation

The present investigation was designed to survey the anatomical variations of the sphenoidal sinus and the possibilities of analysing them roentgenologically Special attention was given to the relationship of the sella turcica to the sphenoidal sinus

Material and Methods

A collection of specimens as well as a series of patients were investigated The former consisted of anatomic specimens from 120 consecutive autopsies in cases without intracranial disease A portion of the base of the skull comprising the body of the sphenoid bone with contiguous structures was removed post mortem Roentgenograms as well as tomograms of the specimens were obtained in axial and lateral projections The anterior wall of the sphenoidal sinus was then opened and the latter inspected The specimens were sawn in two, usually in the sagittal plane but sometimes in the frontal or the horizontal plane and, following removal of the mucous membranes, all specimens were photographed The dimensions of relevant structures in the sinus were determined, the thickness of the anterior wall of the sella turcica was measured at different points with a micrometer and recorded with an accuracy of 0 1 mm Unless otherwise stated, the figures given are based on this collection of specimens

The living material comprised 103 cases of transsphenoid hypophysectomy for metastases from carcinoma of the breast (68 cases), other metastases (10), and diabetes mellitus (25 cases) The findings at preoperative roentgen examination and at operation were compared

Preoperative roentgenograms of the sphenoidal sinus and the sella turcica region were taken in true lateral, antero posterior and full axial as well as oblique projections Thus three lateral films were obtained one with the beam directed true laterally and two with the tube angled 5° cranially and caudally, respectively Another four films were obtained in the axial projection, two with the tube angled 3° cranially and caudally, respectively, for stereoscopy, and

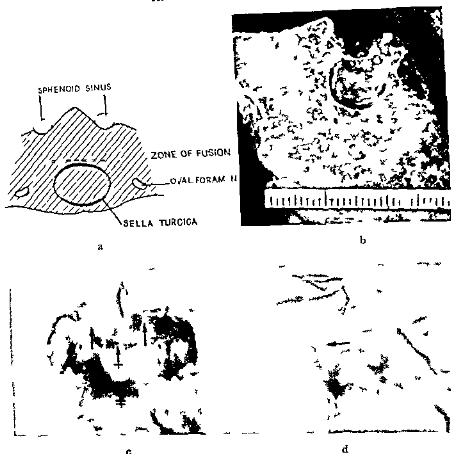


Fig 2 Sphenoidal s nuses of conchal type a) Schematic representation of sphenoid bone hori zontal sect on Small sph noidal inuses s tuated late lly and separated from each other and from the hypophys by a th ck bony wall b) Midl ne sect on th ough sphenoid bone The small spheno dal nuses are not discernible in this section since they are s tuated lateral to this plane The bo e ant r or to the hypophysis partly comp ct and partly cancellous (Scale in mill m tres) c) and d) A ial and lateral roentg nograms of specimen Indistinct small sphenoidal nuses but zones of scle otic and pongy bo e anterior to the hypophysis are clearly dis ernible Spheno dal s nuses (→) ante ior wall of tuberculum s llae (++) dorsum sellae (++)

another two films with the tube angled 5 to 10 towards either side The main purpose of these angled roentgenograms was to secure not only a true rendering of the sphenoidal sinus but to demonstrate any septa which might be present These are sometimes so thin as to be discernible only when they lie in the same plane as the beam and it follows that views in varying projections are often required to establish their number and position The anatomical relations in the sphenoidal sinus and sella turcica regions were further clarified where necessary by tomography For this latter a simultaneous procedure was

generally employed and seven cuts with minimum intervals of 0 5 cm were obtained During the earlier part of this investigation only one tomographic apparatus, producing blurring with linear movement, was available but we subsequently also had the use of a further apparatus, a polytome which produces pluridimensional blurring of irrelevant structures The tomograms were obtained in *antero posterior*, lateral and axial projections but tomograms in oblique projections were obtained in those cases in which relevant structures lay across the plane of the central beam in the standard positions With linear blurring the movement of the tube should preferably be perpendicular to the main direction of the structure to be studied or form an angle of at least about 10 degrees with it

Development on the sphenoidal sinus

In the third month of intrauterine life the primitive sphenoidal sinus appears as an invagination of the nasal mucosa in the posterior portion of the nasal capsule A pouch like cavity is formed in the cartilage by its expansion backwards and downwards, the walls of the cavity being called the sphenoidal concha or the ossicles of Bertin The ossification of this structure begins during the fifth month but not until the fourth year of life does fusion take place with the sphenoid bone proper and pneumatization begin The extent of this pneumatization is best understood with due appreciation of the development of the sphenoid bone (Fig 1)

The body of the sphenoid develops from four symmetric nuclei — two presphenoid centers at the front, for the anterior part, and two postsphenoid centers behind, from which the posterior portion develops The cartilage between these two parts disappears at about the time of birth the zone of fusion between them is at the level of the tuberculum sellae The sella turcica develops solely from the postsphenoid portion (NILUS & LE PICARD 1933) and the bone is formed from lingual centers triangular in shape along either side of the body of the sphenoid The various zones of fusion between the nuclei present a greater resistance to the pneumatization of the growing sinus than do the nuclei themselves (TOLDT 1883, COPE 1916—17, CONGDON 1920 VAN GILSE 1922) The bony septa found in the adult sinus are usually located at the sites of these zones of fusion The sinus extends to the posterior portion of the sphenoid bone before the age of ten years and attains its true size around puberty Extension into the greater wings may occur The spheno occipital synchondrosis, on the other hand, is not ossified until the sixteenth to eighteenth year of life Thereafter the sphenoidal sinus may also expand into the occipital bone

Different types of sphenoidal sinuses

The size of the adult sphenoidal sinus varies widely (DIXON 1937) The sinus has been classified into different main types according to variations in its posterior limits Planes of fusion between nuclei have been used as boundary

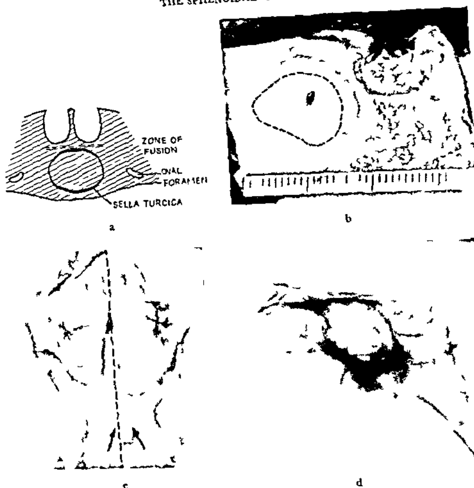


Fig 3 Sph no dal s nuses of p esellar type a) Schematic representation of spheno d bone horizontal sect n The pheno dal s nuses do not extend posteriorly beyond the zone of fus on between the pre and postsphenoidal portions of the body b) M dl ne section th ough spheno d bone right half as v ewed laterally f om ins de Plane of sect on ind cated by the *broken line in (c)* The sphenoidal s nuses are sepa ated from the hypophysis by cancellous bo e The inters nusal septum is p erced Right sphenoidal s nus ma ked by broken line c) Axial *roentgenogram of specimen* B oken l ne indicates plan of sect on of the pr paration Upper bo der of dorsum sellae discern ble (arrows) but not the anterior wall of the sella probably due to unfa orable project on d) Lateral roentgenogram of entire spec men Poster or l mits of right and left sphenoidal sinuses *clea ly shown Anterior* wall of sella turcica about thre t mes as th ck on the r ght as on the left s de

lines and intermediate types have also been reported (Gibson 1912 Cope 1916—17 Congdon 1920 Mahmoud 1958)

With regard to transsphenoid hypophy*sectomy* it is appropriate from a practical clinical standpoint to divide sphenoidal sinuses into three types a conchal a presellar and a sellar type The designations presellar and sellar

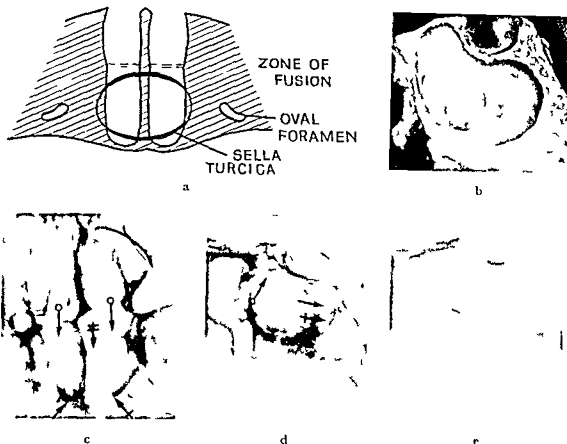


Fig 4 Sphenoidal sinuses of sellar type a) Schematic representation of sphenoid bone horizontal section Both sphenoidal sinuses extend posteriorly beyond the zone of fusion between pre and post sphenoidal centers b) Medial section through sphenoid bone right half as viewed laterally from inside The anterior wall and the floor of the sella appear thicker than in the tomogram (e) due to the fact that the specimen is cut through the attachment of the intersinusal septum c) Axial roentgenogram of specimen Both the right and left sinus extend posteriorly well behind the anterior wall (↔) of sella turcica d) Lateral roentgenogram of entire specimen Posterior wall of the sphenoidal sinus situated further dorsally on the left (↔) than on the right (→) side Carotid prominence (→) e) Tomogram through left sphenoidal sinus Anterior wall of the sella turcica only 0 5 mm Compare this to (d) where the anterior wall and floor of the sella appear to be 1 to 2 mm thick due largely to a slightly oblique projection

which largely correspond to presphenoid and postsphenoid types (Cope), were chosen for the purpose of indicating more distinctly the relationship of the sinus to the sella turcica The boundary between the presellar and the sellar type is defined by a line running perpendicular to the sphenoidal plane through the tuberculum sellae This boundary line, which closely coincides with the plane of fusion of the anterior and posterior parts of the sphenoid bone, is easy to define in roentgenograms

The two sphenoidal sinuses are separated by an intersinusal septum In our investigation no supernumerary sphenoidal sinuses were encountered, nor have we seen them described in the literature

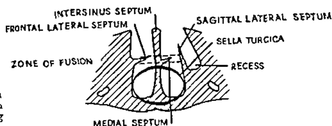


Fig 5 Schematic representation of horizontal section through sphenoid bone showing varying types of septa

Conchal type This type does not extend further posteriorly than the plane of fusion of the sphenoid concha and the body of the sphenoid bone The sphenoidal sinuses are very small and separated from the sella turcica by a cancellous bone wall approximately 10 mm thick (Fig 2) This wall may however, consist partly of sclerotic bone The sphenoidal sinuses are situated well laterally and are separated from each other by a thick bony septum This type is rare in the present series it was found only in three cases (2 5 per cent)

Presellar type This type does not extend posterior to the line of fusion of the presphenoid and postsphenoid portions of the body of the sphenoid (Fig 3) The sella turcica is generally separated from the sphenoidal sinus by spongy bone and the anterior wall of the sella turcica does not bulge into the sphenoidal sinuses In this type the intersinusal septum generally runs in the sagittal plane with no major deviations to either side The pneumatization is not symmetrical and generally one sphenoidal sinus is slightly larger than the other even if both are of the presellar type In our series of specimens a presphenoid type was found bilaterally in 13 cases (approximately 11 per cent)

Sellar type In this type the anterior wall and frequently the floor of the sella turcica appear as a protrusion into the sphenoidal cells As a rule the anterior wall of the sella turcica is exceedingly thin and does not contain spongy bone (Fig 4) Cancellous bone is not infrequently found however in the floor The sellar type is the commonest and in the present series of specimens, occurred bilaterally in 71 cases (59 per cent)

Both a presellar and a sellar type may be found in the same case pneumatization having reached a far more advanced stage on one side often at the cost of the contralateral sinus Such mixed forms with one sinus of the presellar type and the other of the sellar type were found in 33 cases (27 per cent) The total number of cases with at least one sphenoidal sinus of the sellar type thus amounted to 104 (86 per cent)

For determination of the type roentgenographically one axial and one lateral view are usually sufficient Since in the conchal type of sinus (Fig 2, c) and d) the bone around the sinuses is thick and often partially sclerotic, heavily exposed films are required for correct evaluation

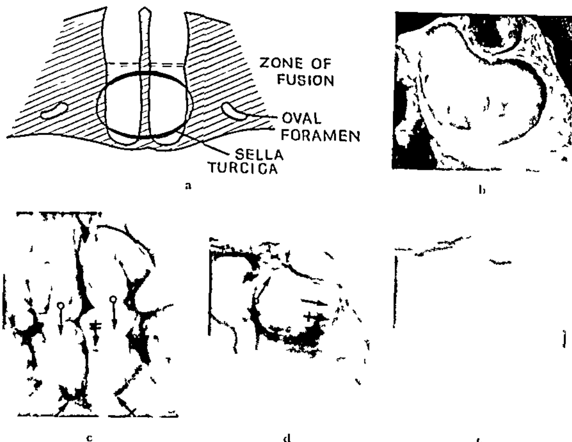


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Fig 7 Intersinusal septum and sagittal lateral septum a) Frontal section through sphenoidal sinuses just anterior to the tuberculum sellae Intersinusal septum (→) as well as sagittal lateral septum (↔) have their posterior superior attachments in the left and right carotid prominences respectively b) The intersinusal septum and sagittal lateral septum may be difficult to differentiate in axial roentgenograms In this case they are both oblique and therefore have double contours c) and d) The two septa may be differentiated by tomography In a section through the anterior part of the sphenoidal sinuses (d) only the intersinusal septum (→) is seen The sagittal lateral septum (↔) reaches the anterior wall of the sinus only in the basal part Anterior wall of sella (↔)

Septa in the sphenoidal sinuses

In addition to the intersinusal septum others extending in different directions may be found They may be classified as follows transverse septum medial septum and lateral septa which are divided into frontal lateral and sagittal lateral

Intersinusal septum This septum, which separates the two sphenoidal sinuses was found in all specimens It lay in the midline throughout its course in 31 cases (approximately 25 per cent) The intersinusal septum usually runs in

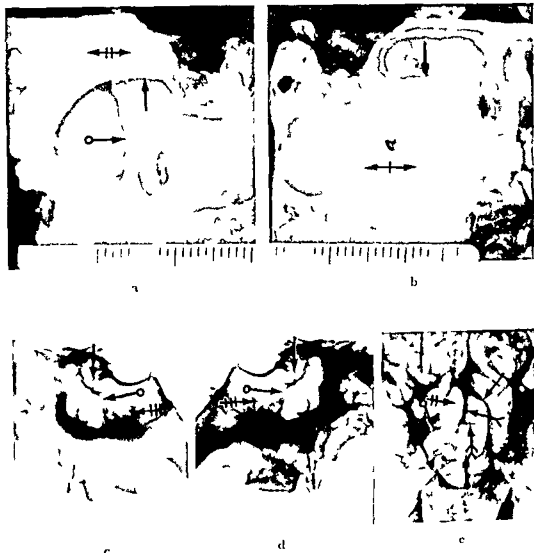


Fig 6 Intersinusal septum a) and b) Medial section through specimen of sphenoid bone right (a) and left (b) halves viewed laterally from inside The intersinusal septum which has been pierced (b) has a scoliotic course in the frontal plane The lower (left) and the upper (right) parts of it thus are vertical and the intermediate part has a more horizontal course Upper vertical part (↔) and horizontal part (→) attached to anterior wall of sella The lower vertical part (↔) is situated so far to the left that it has no direct relationship to the anterior wall A frontal lateral septum (→) is present in right sphenoidal sinus (a) c) and d) Lateral roentgenograms of entire specimen (turned in both directions to facilitate comparison with photographs of specimen) The horizontal portion of the intersinusal septum (→) appears double contoured probably because the roentgen beam is tangential to its different parts The frontal lateral septum (→) and the horizontal portion (→) of the intersinusal septum may together simulate a complete transverse septum e) Axial roentgenogram of specimen The upper vertical portion of the intersinusal septum (↔) may be overlooked leading to misinterpretation of its course The lower vertical part (↔) appears more distinct than the upper vertical part as the former lies more in line with the beam Vomer and rostrum sphenoidale (→) Anterior wall of sella (→) Uppermost part of dorsum sellae (→)

If the sinuses are indistinct in conventional roentgenograms, their boundaries may be determined from tomograms in different projections



Fig 9 Transverse crest Ordinary lateral roentgenogram (a) and lateral tomogram (b) The thin transverse crest (→) has its attachment relatively low in anterior wall of the sella. Bony wall running vertically to floor of sphenoidal sinus is not a part of a complete transverse septum but a frontal lateral septum (↔) (c) and (d) Axial and frontal tomograms The transverse crest extends completely across the anterior wall Intersinusal septum (⇸)

in some degree with the movement of the tube irrespective of the patient's position (Fig 7)

The intersinusal septum like most of the other septa in the sphenoidal sinus, generally emerges clearly in a conventional axial view, and from such a view, with slight differences in angulation determinations may be made not only of deviations from the sagittal course but also with some accuracy the degree to which the septum slopes vertically Such films may also be of value in determining the true course of the intersinusal septum because so frequently it is covered by the vomer and the rostrum sphenoidale in the true axial projection If the septa or lateral walls of the sphenoidal sinus are not clearly seen owing to such superimpositions as gas in the pharynx, the vomer the posterior

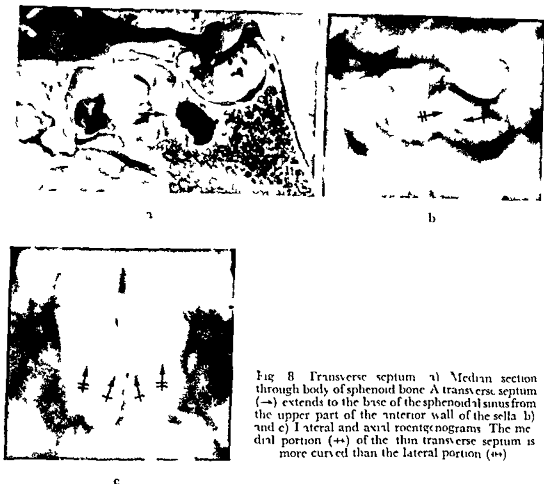


Fig 8 Transverse septum a) Median section through body of sphenoid bone A transverse septum (→) extends to the base of the sphenoidal sinus from the upper part of the anterior wall of the sella b) and c) Lateral and axial roentgenograms The medial portion (++) of the thin transverse septum is more curved than the lateral portion (+++)

the midline only anteriorly The posterior part often deviates more or less to the sides and is accordingly often attached laterally to the anterior wall of the sella or sometimes as far laterally as in the carotid prominence, i e in the most anterior portion of the carotid groove This variant was found in 24 cases in our series (20 per cent) The septum not infrequently has a 'scoliotic' appearance in both the sagittal and the frontal planes It occasionally has a marked tilt in relation to the vertical plane, that is, with its upper and lower borders situated on opposite sides of the middle line In such cases the septum assumes a more or less horizontal course (Fig 6)

The intersinusal septum is difficult to distinguish in ordinary antero posterior films owing to superimposed structures These may be eliminated by tomography, by which method fairly precise information as to the position and tilt of the intersinusal and other septa may be obtained Pluridimensional blurring is desirable, *in the frontal projection or in modifications of the frontal pro* jection enforced by the main course of the intersinusal septum, the superimposed structures (ethmoid cells, nasal septum conchae etc) can seldom be entirely eliminated by linear blurring for their extension invariably coincides

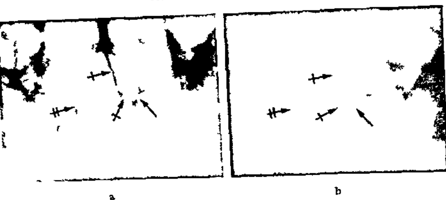


Fig 11 Medial septum a) Axial roentgenogram b) Axial tomogram The medial and intersinusal septa meet at the level of the anterior wall of the sella turcica A medial septum constitutes the medial portion of a complete transverse septum (cf fig 8) In this instance both the medial septum (→) and the sagittal lateral septum (↠) are fairly thick Intersinusal septum (+→)

hickness of the anterior wall at the attachment of the transverse septum may be estimated in a conventional lateral view but is best determined in lateral tomograms which may also show whether the septum is attached to the whole or only to a part of the anterior wall of the sella turcica The extension in the frontal plane may be estimated with greater certainty from a p tomograms (Fig 9d)

A transverse septum or crest may be confused with other bony structures running across the anterior wall thus the intersinusal septum as mentioned before may run a partly horizontal course in its posterior part and posterior ethmoid cells may extend backwards into the body of the sphenoid bone usually above the sphenoidal sinus and are then termed spheno-ethmoid cells The floor of such cells may be attached to the anterior wall of sella turcica

Spheno-ethmoid cells may usually be identified without difficulty in a conventional lateral view The wall of the cells may be more distinct in a lateral tomogram which will show that the cells continue forwards into the ethmoid bone beyond the anterior wall of the sphenoidal sinus (Figs 10 and 15) A transverse septum or crest does not reach the anterior wall of the sphenoidal sinus and hence is unlikely to be confused with the wall of a spheno-ethmoid cell The differentiation between a transverse crest and an intersinusal septum that is attached horizontally to the anterior wall of the sella turcica is not however always possible from conventional roentgenograms alone tomography in the frontal plane is also required

The zone of fusion between the pre and postsphenoidal centers of the body of the sphenoid may be manifested as septa other than transverse septa (Fig 5)



Fig 10 Spheno ethmoid cell a) Median section through specimen of sphenoid bone right half viewed laterally from inside Above the sinuses an unusually large spheno ethmoid cell (→) extending posteriorly to anterior wall of sella The floor of the cell has a wavy course and is tilted so that the right portion (↠) is higher than the midline (Below the spheno ethmoid cell lies the intersinusal septum (⇸) which is situated entirely in the right half of the sphenoid bone and posteriorly is deviated markedly to the right) b) Lateral tomogram of entire specimen showing extension of the spheno ethmoid cell which anteriorly continues into the ethmoid bone (The tomographic section is almost in the midline but in spite of this the right part of the floor of the cell is also well shown probably because it has remained in the plane of the central beam during the greater part of the tube movement)

parts of the concha, the hyoid bone etc, tomography in this projection can be of great value *If a tomograph with linear blurring is employed it is usually* advantageous to move the tube in the frontal plane since most of the above mentioned structures have a more or less sagittal direction

Transverse septum Bony septa of various shapes and sizes may persist in the adult at the sites of the zone of fusion between the postsphenoidal and pre *sphenoidal centers One of them is the* transverse septum and may occur either in one or in both of the sphenoidal sinuses (Fig 8) It is attached usually to the upper part of the anterior wall of the sella turcica, from which it first extends obliquely downwards and forwards, then more directly downwards to a point near the floor of the sphenoidal sinus, close to the intersinusal septum it becomes somewhat convex posteriorly If only the whole or part of the upper more horizontal portion persists it is called the transverse crest (Fig 9) At the attachment of such a septum or crest the anterior wall is locally thickened and usually contains cancellous bone In our combined series of patients and specimens, three transverse septa and eight transverse crests were recorded

Both the upper, more horizontal and the lower, more vertical portions of the transverse septum are evident in the lateral projection (Fig 8b) Axial views, on the other hand, reveal only the lower vertical part, which frequently is so thin that an optimal projection is required for its demonstration (Fig 8c) The



Fig 13 Sag ttal lateral septum Small right and a very large left inus with a th ck sagittal lateral septum resembl ng the intersinusal septum *Upper row* Median sect on through sphenoid bone right and l ft hal es respecti ely viewed laterally from ins de In the r ght half the posterior l m t of the ght sphe o dal s nus is indicated by a broken line In the left half the posterior boundary of the lateral r cess i e that part of the left sinus between the sagittal lateral septum (↔) and lateral all of the sinus ind cated by a broken line The posterior super or parts of the inters nusal (→) and lateral (↔) septa have the r attachments in the right and left ca otid p ominences espect ely *Lower row* Lat al roentgenograms of the ent re specimen tu ned towards either s de to facil tate comparison with the photographs *Ri ht* Ax al roentgenogram

In this ca e the sagittal lateral (↔) and the ntersinusal septum (→) cannot be different ated in ax al and lateral v ews alone The port on of the sagittal lateral septum which s anterior to the sphen oidal l mbus (↔) is only half as h gh as the inters nusal septum Nevertheless it has approx mately th same dens ty n the axial v ew as the inters nusal septum In the lateral view the anterior border of the lateral septum is barely d scernible Differentiation of these septa therefo e requires frontal (cf fig 7) or axial tomograms Anterior wall of sella turcica (→) Posterior boundary of right (↦) and left (↦) spheno dal sinus Posterior boundary of recess on left s de (→) Med al wall of left optic fora men (→)

lateral septum is not so distinct as the intersinusal septum In doubtful cases these two structures may be differentiated by axial or frontal tomography which will show that the anterior portion of the lateral septum is not in contact with the anterior wall of the sinus throughout its cranio caudal length (Fig 7)

Anterior wall of the sella turcica

The thickness of this wall is dependent upon the degree of backward exten sion of the sphenoidal sinus In the conchal type (Fig 2) the anterior wall may exceed 10 mm in thickness In the sellar type the anterior wall is almost ex clusively composed of thin compact bone except for a small rim of cancellous bone at the attachment of the intersinusal septum (Fig 4) In this material of specimens the compact portion of the anterior wall had a thicknes of 0 5 ± 0 21



Fig 12 Lateral septa Frontal section through sphenoid bone just anterior to the tuberculum sellae viewed from the front showing both a sagittal (→) and a frontal lateral septum (↔) The intersinusal septum (↔) is arch shaped The sagittal lateral septum has its posterior superior attachment in the right carotid prominence The frontal lateral septum is attached above partly to the left carotid prominence Rostrum sphenoidale and vomer (→) Right (→) and left (←) carotid prominences

Medial septum If the medial portion of this zone persists a medial septum, usually unilateral, will arise from the anterior wall of the sella turcica at the site of attachment of the intersinusal septum (Fig 11) Fourteen medial septa were found in our series

Frontal lateral septum This septum is a lateral residue of the aforementioned barrier between the pre and postsphenoidal centers of the body of the sphenoid bone (Fig 5) Since it is situated largely in the frontal plane, it is termed the frontal lateral septum (Figs 6, 9 and 12) It has its attachments in the lateral wall and the base of the sphenoidal sinus, and its free edge is directed towards the intersinusal septum

Sagittal lateral septum Another type of lateral septum is located at the site of fusion of the body of the sphenoid bone and the lingual center Such a septum runs almost in the sagittal plane with its free border directed forwards and somewhat medially, and is here called the sagittal lateral septum, lateral to it lies the lateral recess The posterior attachment of this septum is situated wholly or partially in the most anterior portion of the carotid groove the carotid prominence (Figs 7 and 12)

Lateral septa are common In the present series they were found in 106 sphenoidal sinuses (44 per cent) The great majority were of the sagittal type, and in most cases short If a sagittal lateral septum is unusually large and extends to the anterior wall of the sinus with its upper and/or lower edge, it may be mistaken in axial views for an intersinusal septum (Figs 7 and 13)

A sagittal lateral septum may be even nearer the midline than the intersinusal septum It is usually possible to distinguish between these two septa in ordinary roentgenograms As a rule, the most anterior part of a sagittal



Fig 13 Sagittal lateral septum Small right and a very large left sinus with a thick sagittal lateral septum resembling the intersinusal septum *Upper row* Median section through sphenoid bone right and left halves respectively viewed laterally from inside In the right half the posterior limit of the right sphenoidal sinus is indicated by a broken line In the left half the posterior boundary of the lateral recess i e that part of the left sinus between the sagittal lateral septum (↔) and lateral wall of the sinus is indicated by a broken line The posterior superior parts of the intersinusal (→) and lateral (↔) septa have their attachments in the right and left carotid prominences respectively *Lower row* Lateral roentgenograms of the entire specimen turned towards either side to facilitate comparison with the photographs *Right row* Axial roentgenogram

In this case the sagittal lateral (↔) and the intersinusal septum (→) cannot be differentiated in axial and lateral views alone The portion of the sagittal lateral septum which is anterior to the sphenoidal limbus (↔) is only half as high as the intersinusal septum Nevertheless it has approximately the same density in the axial view as the intersinusal septum In the lateral view the anterior border of the lateral septum is barely discernible Differentiation of these septa therefore requires frontal (*cf fig 7*) or axial tomograms Anterior wall of sella turcica (→) Posterior boundary of right (↔) and left (↔) sphenoidal sinus Posterior boundary of recess on left side (→) Medial wall of left optic foramen (→)

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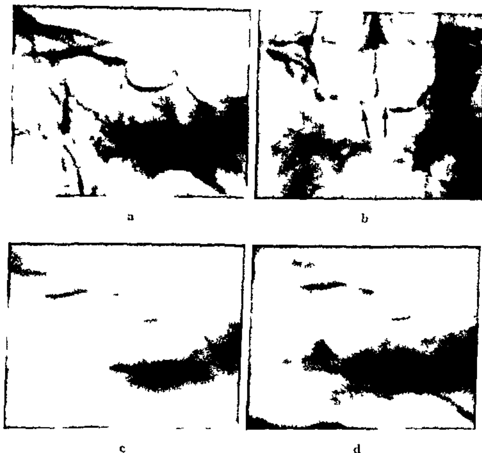


Fig 14 Varying thickness of anterior wall of sella turcica a) and b) Lateral and axial roentgenograms c) and d) Lateral tomograms through the right and left parts of sella Right anterior wall (c) of the sella is 2 to 3 mm thick while the left anterior wall (d) is 1 to 2 mm thick In the axial view the thickness of the anterior wall (→) is difficult to evaluate because of superimposed structures (posterior wall of the sinuses situated below the sella)

mm Variations in the thickness of the anterior wall of surgical importance occur in the presellar type and in cases with one sphenoidal sinus of presellar and the other of sellar type The wall as a rule is thinnest on the sellar side

A lateral view of the pituitary fossa should convey a general idea of the thickness of the anterior wall and show if there are variations in the thickness and the distribution of these in the vertical plane Oblique lateral views may also provide information regarding the anterior wall in the frontal plane

An axial view shows the anterior wall, especially the part consisting of compact bone, provided it is so obtained that the central beam coincides with a plane through the anterior wall of the sella turcica The anterior wall as a rule can therefore be demonstrated in axial projections except in those cases in which it has an extremely sloping course The lateral boundary of the anterior wall is marked by the most anterior parts of the carotid grooves and, if these also are discernible in the axial view, the extension of the anterior wall in the

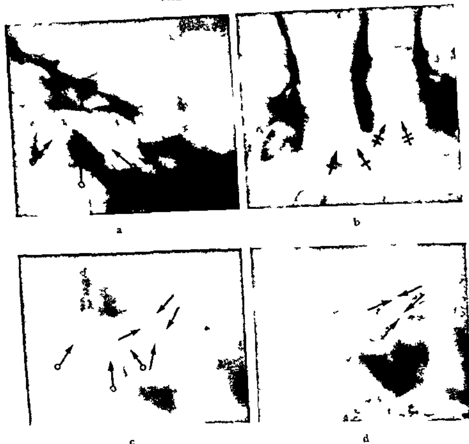


Fig 15 Metastases from carcinoma of breast to sphenoid bone causing asymmetric thickening of the anterior wall (→) and floor of sella a) and b) Lateral and axial roentgenograms Lateral tomograms through the right (c) and left (d) parts of sella Metastases involve most of body of sphenoid The tomograms reveal that the right half of the anterior wall of the sella turcica is much thicker than the left The axial view indicates that the right sphenoidal sinus (↔) extends further posteriorly than the left (↔) When the anterior wall varies in thickness its thinnest part usually coincides with the sinus which has the greatest posterior extension In this instance the reverse is the case The large spheno-ethmoid cell (○–) on the right side is clearly visible only in the lateral tomogram

frontal plane may be determined (For details the reader is referred to a later article on this subject)

It is usually possible by comparing the appearance of the anterior wall in lateral and axial projections to gain a fairly good idea of the topography of the anterior wall though tomography (preferably in a lateral projection) will provide more detailed information Such an examination is usually necessary for correct estimation when the anterior wall is irregularly thickened especially when it has a sloping course which prevents its demonstration in an axial



Fig 16 Tuberculum sellae (→) situated considerably below the roof of the sphenoidal sinuses a) Median section through specimen of sphenoid bone b) Lateral roentgenogram of entire specimen The optic groove slopes steeply downward and the tuberculum sellae is therefore situated far below the roof of the sphenoidal sinuses Sphenoidal limbus (↠)

projection, or when evaluation is complicated by the occurrence of septa having their attachments to the anterior wall, e g transverse and medial septa

The majority of hypophysectomies are performed in cases of metastases from carcinoma of the breast A few patients in the present series had sphenoid bone metastases in and around the sella turcica These lesions frequently alter the original anatomy, in some cases producing irregular thickening of the anterior wall and the floor of the sella turcica (Fig 15)

The limbus sphenoidalis, which forms the most anterior boundary of the optic groove, may be confused in axial views with the anterior wall of the sella turcica This applies to cases in which the anterior wall is flat and hence either indistinct or invisible whereas the limbus lies relatively high and is thus well defined The lateral continuation of these structures affords guidance for the differentiation of the limbus and the anterior wall in axial views The anterior wall continues laterally in the carotid prominence which is defined as an anteriorly convex wall of compact bone The lateral continuation of a high limbus in the medial wall of the optical canal is often also clearly visible (Fig 13)

The uppermost part of the dorsum sellae may sometimes be identified in axial views as a thin, transverse cortical layer, notably when the dorsum is completely pneumatized This structure is situated however so far posteriorly that it is unlikely to be confused with the anterior wall of the sella turcica (Figs 4 and 6)

The area between the limbus sphenoidalis and tuberculum sellae, i e the optic groove or 'area praesellaris' forms a highly variable angle with the sphenoidal plane In a few cases it slopes very steeply downward and may be

mistaken for the upper part of the anterior wall of the sella turcica in such cases the tuberculum sellae is situated relatively far below the roof of the sphenoidal sinus On piercing the anterior wall of the sella turcica an operator unaware of the true anatomy may easily go too high and enter the intracranial cavity above the diaphragma sellae into the region of the cisterna chiasmatica and the optic chiasma (Fig 16) Ordinary roentgenography in the lateral plane, possibly in conjunction with tomography will disclose this variant

Discussion

Prior to transsphenoid hypophysectomy the following data should be established roentgenologically (1) The type of sphenoidal sinuses and thickness of the anterior wall of the sella turcica (2) the position of the intersinusal septum (3) the presence of septa that may impede the operation

1 The relationship of the sphenoidal sinus to the sella turcica is inconstant the former varying greatly in size and shape According to PEELE (1957), agenesis of the sphenoidal sinuses is reported in the literature We did not encounter it, nor did DOUGLAS (1906) CANUYT & TERRACOL (1925), VAN GILSE (1926) SCHAEFFER (1936) VAN ALYEA (1941) Sphenoidal sinuses are probably always present but in the conchal type they may be so small as to elude detection even on anatomic dissection

Conchal sphenoidal sinuses occur in only a low percentage of cases The sinuses are then separated from the hypophysis by a preponderantly cancellous bony wall By virtue of its thickness as well as its ready tendency to bleed the presence of this type should be considered a contra indication to transsphenoid hypophysectomy (HAMBERGER et coll)

In the second main or presellar type the sphenoidal sinuses are usually also separated from the hypophysis by cancellous bone though it is seldom more than a few millimeters thick The anterior wall of the sella turcica is not well defined in the sphenoidal sinuses hence a more difficult operation may be anticipated This type of sphenoidal sinus does not directly contra indicate transsphenoid hypophysectomy (HAMBERGER et coll) If the anterior wall is more than 1 mm thick it consists of cancellous bone, when its thickness varies it is of great importance to know where the thinnest part is situated for the wall may be initially perforated at that point In such cases roentgen analysis of the anterior wall thickness in the different parts requires tomography variations in thickness may then be determined with an accuracy of approximately half a millimeter

The third main or sellar type is ideal for hypophysectomy and is the commonest The anterior wall of the sella turcica is very thin usually not more than a few tenths of a millimeter and thus presents no technical problems Moreover, not only the anterior wall but frequently the floor of the sella turcica are

distinctly marked in the sphenoidal sinuses It is surgically justifiable to classify a case as sellar if one of the sphenoidal sinuses is of the sellar type On this basis the sellar type occurred in 86 per cent of the present series of specimens This figure appears to be somewhat higher than corresponding frequencies in the literature (GIBSON, COPE, CONGDON, MAHMOUD)

2 The position of the intersinusal septum posteriorly plays an important role in the surgical approach to the hypophysis the usual route is through the sphenoidal sinus which is largest at the level of the anterior wall and floor of the sella turcica

Immediately lateral to the hypophysis are the cavernous sinus and the internal carotid artery The width of the anterior wall of the sella turcica is, on an average, 11 (7 to 16) mm In hypophysectomy the operator therefore has only a relatively small area available and he should consequently be able to recognize the lateral limits of the anterior wall in relation to the attachment of the intersinusal septum, this latter being easy to identify at operation This attachment provides no direct clue to the midpoint, only in about one fourth of the cases do these points coincide, indirectly, however, the attachment affords useful guidance, since at the preoperative roentgen examination it may be localized with great accuracy in relation to the midpoint of the anterior wall In approximately one fifth of the cases the attachment is onto the carotid prominence and, since the latter may bulge into the sphenoidal sinus in much the same way as the sella turcica, there is a possibility of confusion between these two structures It should also be pointed out that a much developed sagittal lateral septum may be mistaken in roentgenograms for the intersinusal septum with consequent errors in orientation

3 A complete transverse septum is rare The septum is generally confined to one sinus and the surgical approach should preferably be through the contralateral sinus Since a transverse septum impedes orientation in the sinus and since its position helps to determine the operative approach, it should be identified preoperatively, otherwise a transverse septum or crest is of surgical significance only in so far as it has its attachment in the anterior wall and causes local thickening

A well developed medial septum may also complicate the operation as troublesome bleeding may occur from the cancellous bone which lies at its attachment to the anterior wall of the sella turcica and to the intersinusal septum Roentgenologic identification of such a septum prior to operation is accordingly of importance A frontal lateral septum, on the other hand, does not influence the surgical technique

Since the anatomical variations of the sphenoidal sinus have a decisive bearing on the operability and the surgical procedure, preoperative roentgenologic analysis is often necessary for the planning and successful conduct of

transsphenoid hypophysectomy Our experience of this series indicates that all anatomic variants of surgical significance may be analyzed by roentgen examination on the general principles now outlined

SUMMARY

A total of 120 anatomic specimens of the body of the sphenoid bone were examined by means of conventional roentgenograms and tomograms and dissected The anatomical and roentgenologic findings were correlated both in the dissection material and in a clinical series of 103 patients Special attention was given to those structures and variations that are important in transsphenoid hypophysectomy

ZUSAMMENFASSUNG

Insgesamt 120 anatomische Preparate des Corpus sphenoidale wurden mit Hilfe von konventionellen Rontgenogrammen und von Tomogrammen untersucht und seziert Die anatomischen und rontgenologischen Befunde wurden sowohl im Dissektionsmaterial als auch in einer klinischen Reihe von 103 Patienten mit einander verglichen Spezielle Aufmerksamkeit wurde den Strukturen und Variationen gewidmet welche bei der transsphenoidalen Hypophysektomie von Bedeutung sind

RÉSUMÉ

Les auteurs ont radiographié tomographié et disséqué 120 pièces anatomiques de corps de l os sphénoide Les résultats anatomiques et radiologiques ont été comparés sur les pièces disséquées et sur une série clinique de 103 malades Les auteurs ont spécialement étudié les structures et les variations anatomiques qui sont importantes pour l hypophysectomie transsphénoidale

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FROM THE DEPARTMENT OF PHARMACOLOGY (DIRECTOR PROF B UVNAS) KAROLINSKA INSTITUTET STOCKHOLM SWEDEN

RENAL CIRCULATORY INSUFFICIENCY AFTER RENAL ANGIOGRAPHY

An experimental study

by

PERCY LINDGREN

Considerable attention has been focused on the damage caused by the intravascular injection of contrast media in renal and cerebral angiography (for references see OLSSON 1955 and IDBOHRN 1956) Albuminuria cylindruria, elevated NPN and in isolated cases, oliguria and grave renal insufficiency have all been observed following the passage of large quantities of contrast medium through the renal circulatory system fatalities have also been reported

For some time animal experimental studies have been carried out in this laboratory on the pharmacodynamic properties of different roentgen contrast media with particular reference to their effects on the circulatory system A noteworthy observation in these studies has been the marked local vasodilatation that has occurred after the intra arterial injection of sodium acetrizoate the blood flow being greatly increased both in angiography of the arteries of the intestines and extremities (LINDGREN & TORNELL 1958) and in carotid angiography (KAGSTROM LINDGREN & TORNELL 1958) The chemically similar roentgen contrast media sodium diatrizoate and sodium diprotrizoate also have vasodilatory properties although not nearly to the same extent as those of sodium acetrizoate

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Fig 1 Cat 1 8 kg Dial 50 mg/kg Decrease in renal blood flow on repeated arteriography with sodium acetrizoate (1) (2) and (3) Injections of 0 8 ml Na acetrizoate 50 Between each injection the scale of the renal blood flow (i e the speed of the interval recorder) was changed

number of such small doses were given at short intervals (2 to 3 min) or when larger quantities (0 4 to 0 8 ml i e approximately 0 2 to 0 5 ml/kg) were injected reduction of the blood flow usually occurred The decrease in the blood flow takes place very soon after the passage of the contrast medium through the kidney Even when a larger dose (0 4 to 0 8 ml) was administered the blood flow was often not notably changed, but when the same dose had been repeated two or three times, there was always a definite decrease in the renal blood flow

The results of such an experiment are shown in Fig 1 A dose of 0 8 ml sodium acetrizoate was injected into the left renal artery of a cat weighing 1 8 kg The blood flow dropped immediately from 14 ml/min to approximately 5 ml/min After a few minutes a gradual increase took place although not a return to the initial level The flow became stabilized at about 9 ml/min Two additional injections of the same quantity of medium caused further reduction in the blood flow which was only 0 5 ml/min after the third injection or only 3 per cent of the initial flow

Considering earlier experiences in which a marked vasodilator effect was produced by sodium acetrizoate on other vascular regions the results described are surprising However several additional similar experiments confirmed the observation The significance of the dosage has already been discussed The animals exhibited rather wide individual variations in sensitivity estimation of a more exact dose response ratio is unfortunately impossible because of the small material

A few experiments were carried out with recording of the blood flow in each renal artery partly to preclude the possibility that the recording apparatus might contribute to the occurrence of the circulatory insufficiency in the kidney

It was considered that a study of the effect of sodium acetrizoate on the renal circulation during and after angiography would prove an interesting complement to the aforementioned investigations Since considerable differences between the vascular effects of sodium acetrizoate and sodium diatrizoate had previously been observed, the latter was also included in the investigation

Methods

The material consisted of 14 cats weighing from 1 0 to 2 3 kg (average 1 6 kg) anesthetized with Dial in a dose ranging from 50 to 70 mg/kg The left renal artery was exposed for a distance of 1 to 2 cm from its origin from the aorta via a 5 cm incision in the left flank immediately below the ribs, since the operation was entirely retroperitoneal, all injury to the abdominal organs was avoided The right renal artery was also exposed via the same incision in the left flank in those cases in which a recording of the flow in each kidney was required

A change in the technique used earlier for photo electric drop recording of blood flow (LINDGREN & UVNAS 1954 and LINDGREN & TORNELL 1958) made it possible to record the blood flow in the renal artery The modified method, the principle of which is that the drops fall into a medium of silicon oil instead of air as earlier, permits the recording of a flow of blood of up to 40 ml/min as against only about 15 ml/min with the former method (The blood flow in a renal artery in a small cat is usually about 10 to 20 ml/min)

The blood flow in the vessel is directed via an extracorporeal loop consisting of thin plastic tubes and a drop chamber of plexiglass, all enclosed in a thermo statically controlled (38° C) water jacket The drops are recorded by a photo cell, which drives an ordinate recorder The method requires heparinization of the animal, which is effected with 25 mg/kg heparin given intravenously in a 5 % solution Intra arterial injections are administered peripheral to the drop chamber via a thin plastic tube inserted as a collateral to the blood carrying tube The injections are always given so that the volume per unit of time is the same as that of the blood flow so that the contrast medium enters the kidney practically undiluted The blood pressure is recorded with an ordinary mercury manometer connected with the carotid artery

The following contrast media were investigated sodium acetrizoate 50 % (Triurol, Leo) and *sodium diatrizoate* 50 % (*Hypaque*, Winthrop) (The former is also available as i a Acetiodone, Diaginol, Rheopak and Urokon, and the latter as Nycopaque and Urographin)

Results

Sodium acetrizoate Single intra arterial injections as small as 0 1 to 0 2 ml of the contrast medium caused little or no change in the renal circulation although an increase of 10 to 30 per cent in the flow could sometimes be observed When a

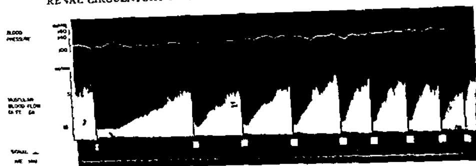


Fig 2 Cat 2 ? kg Dial 65 mg kg Increase in muscle blood flow on intra arterial injection of sodium acetrizoate (1) to (8) inclusive 0 8 ml Na acetrizoate 50 (9) 0 8 ml saline (The short initial decrease in flow during the injection time is not a real decrease but due to the injections being given peripheral to the drop chamber)

kg bodyweight 0 8 ml into the renal artery is a very large dose — it corresponds to about 35 ml in a human being In order to investigate if larger and repeated doses of sodium acetrizoate could give rise to other reactions, in a muscle region for example than the blood flow increases described earlier the following control experiment was performed (Fig 2) The flow in the femoral artery in a cat was recorded by the accepted method and 0 8 ml sodium acetrizoate was injected at least eight times at brief intervals between each injection Each injection caused vasodilatation with an increase in the flow A certain degree of tachyphylaxis was observed but no tendency to a decrease in flow of the type seen in the kidney was noted The experiment suggests that the reaction of the renal circulation to sodium acetrizoate is specific

Sodium diatrizoate This contrast medium was injected in four experiments with recording of the flow in the left renal artery Notwithstanding that large doses (0 8 ml) were given repeatedly no noteworthy changes in the blood flow occurred To preclude the possibility of individual variations two experiments were performed with recording from both sides simultaneously Sodium acetrizoate was injected into the left renal artery and sodium diatrizoate into the right renal artery at the same time and in the same doses One of these experiments is illustrated in Fig 3 A successive decrease occurred in the flow through the left kidney and when eight injections each of 0 4 ml, had been given the circulation had almost ceased On the right side where eight parallel injections of sodium diatrizoate had been given no change took place

Postmortem examination Both kidneys were removed for inspection in all animals In the kidneys subjected to intra arterial injections of sodium acetrizoate and through which the blood flow at the termination of the experiment was less than 30 per cent of the initial level extensive macroscopic changes were observed The kidney was markedly enlarged with a greatly distended edem

demonstrated and partly so that any reactions in the other kidney as a result of the comparatively large quantities of medium entering the systemic circulation could be studied The contrast medium was injected into the left renal artery in repeated doses of 0 4 ml until the flow had practically stopped, in conformity with the experiments illustrated in Figs 1 and 3 In the beginning of the experiments a slight increase in the flow occurred simultaneously in the right kidney The experiments were continued for two hours, during which time the flow on the right side remained constant at slightly above the initial level

It is of considerable importance to know whether the decrease in the flow is of a temporary or protracted character In the experiment shown in Fig 1 the course was followed for an hour longer than stated No increase in the blood flow was demonstrable The same observation has been made in other similar experiments, i e when the blood flow decreased to a mere fraction of the initial level, no improvement ever occurred during the 1 to 3 hour period the experiment could be continued In other experiments in which only one or two injections were given and in which the flow became stabilized after 5 to 10 minutes at about 50 per cent of the initial level, very little additional improvement took place during the next hour In brief it may be said that the course of the reaction during the first 5 to 10 minutes was decisive the level the blood flow had then assumed remained unchanged as a rule during the remainder of the experiment if no further injections were given

The question arises as to whether the decrease observed in the renal circulation is due to a vasoconstriction in either the arterioles or larger arteries caused by sodium acetrizoate, or whether there are other causes This fundamental problem will be discussed in greater detail later but in the meantime some observations regarding this problem may be reported Decapsulation was performed in one case in which injections of sodium acetrizoate (0 4 ml) had resulted in a reduction of the renal blood flow to about 40 per cent of the initial level The flow then increased immediately to approximately 70 per cent but not further, and within 15 minutes a drop to the 40 per cent level occurred Operation revealed that the capsule was markedly distended as in renal swelling and increased intracapsular pressure This could explain the temporary increase in the flow on decapsulation That an increase in the intracapsular pressure had occurred was also clearly shown by the postmortem examination (see later)

During the earlier investigations, reviewed in the introduction, on other vascular regions (e g femoral arteries, carotid arteries) the intra arterial injections were usually carried out with smaller quantities (0 05 to 0 2 ml) of contrast medium since even such doses produced marked effects Considered in relation to the flow in milliliters per minute in the vessel in question a dose of 0 8 ml of sodium acetrizoate injected into a renal artery cannot be regarded as significantly larger It should be pointed out however, that expressed per

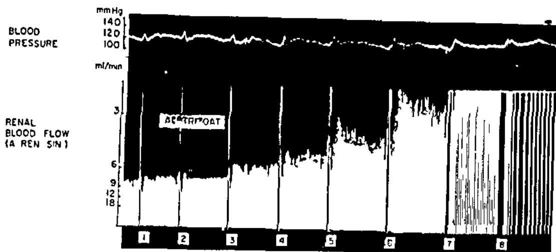
Discussion

The decrease in the blood flow through the kidney after the intra arterial injection of sodium acetrizoate may seem surprising considering the considerable vasodilatory effects of that contrast medium in other tissues such as the skeletal musculature skin small intestine and brain (LINDGREN & TORNELL 1958 and KAGSTROM LINDGREN & TORNELL 1958) It would be extremely remarkable if the medium had a vasoconstrictory effect on renal vessels and a vasodilatory action on other vessels and no basis for such an assumption was demonstrated On the contrary the observations described may well be explained by a vasoparalytic effect of sodium acetrizoate even on renal vessels The renal circulation differs appreciably from that of other tissues, the kidney has a very large blood flow per gram of tissue it consists of but slightly elastic parenchymatous tissue and it is surrounded by an inflexible capsule Consequently if considerable vascular paralysis with elements of permeability impairment occurs the prerequisites are at hand for a rapid rise in the intracapsular and intrarenal pressure The result may then be a secondary decrease in the blood flow with consequent hypoxia which in turn may contribute to an exacerbation of the condition There is much evidence pointing to the existence of such a mechanism For instance a temporary improvement in the circulation was observed after decapsulation Moreover at postmortem examination obvious edema with a considerable increase in weight of the kidney injected with sodium acetrizoate was demonstrated Nor should we *forget that* small doses of sodium acetrizoate caused an increase although a slight one in the blood flow

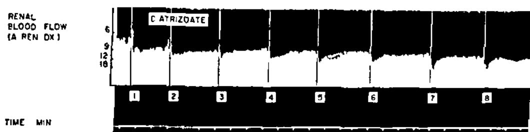
Studying the angionephrographic effect in dogs on selective renal angiography EDLING and HELANDER (1959) attributed abnormal findings to a disturbance in the circulation and an impaired function of the excretory system As these changes in the intrarenal circulation could not be correlated to the dose administered the authors discussed a reflex influence of the contrast medium or of the catheter

Earlier investigations of the pharmacodynamics of sodium acetrizoate have shown that impaired permeability with injuries to the blood brain barrier (BROMAN & OLSSON 1956) and an *increase in the* intracranial pressure (KAGSTROM & LINDGREN 1960) can occur after carotid angiography It is not improbable that similar permeability impairment occurs in the kidney

The anatomic findings agree with observations by BERG IDBOHRN & WENDEBERG (1958) who studied histologically the occurrence of renal damage in rabbits after angiography with different contrast media They stated, without giving quantitative data however, that in some cases the kidney examined was swollen and heavier than the contralateral organ at microscopic examination albuminous exudation into Bowman's capsule and exudative tubular degeneration among changes were present They also discovered a clear



a



b

Fig 3 Cat 1 5 kg Dial 60 mg/kg Simultaneous recording of the blood flow in the left and right kidneys Comparison of effects of repeated arteriography with sodium acetrizoate (left) and sodium diatrizoate (right) 8 injections (0 4 ml) of each contrast medium were given

atous, and cyanotic capsule The cut surface revealed extremely edematous tissue with diffuse hemorrhages in both the cortical and the medullary substance The left kidneys injected with sodium acetrizoate showed a marked increase in weight In 9 cats (1 0 to 2 3 kg) given intra arterial injections of sodium acetrizoate into the left kidney (in amounts sufficient to reduce the renal blood flow to below 30 per cent of the original level), the mean weight of this organ was 8 4 g, the corresponding value for the right kidney was 6 9 g i e the left kidney weighed not less than 25 per cent more In a control series not given any contrast media at all no significant difference was found between the weight of the two kidneys (Unfortunately, the kidneys were not weighed until after fixation, some shrinkage had therefore probably taken place and the weights did not correspond exactly to the in vivo conditions) The kidneys were fixed in 10 % formalin for later microscopic examination

1. In single small doses (0.1 to 0.2 ml) sodium acetrizoate produced no change or only a slight increase in the renal blood flow.

2. When larger doses of sodium acetrizoate (0.4 to 0.8 ml) were injected, a decrease in the blood flow occurred. With repeated injections the flow was successively reduced until it finally almost ceased after a total of 2 to 5 ml had been given.

3. Postmortem macroscopic examination showed a marked increase in the weight of the injected kidney, which was on an average 25 per cent heavier than the contralateral kidney and revealed edematous cyanotic renal tissue.

4. The circulatory insufficiency observed was interpreted as secondary to factors including red cell agglutination and obstructed renal capillaries, edema and increased interstitial and intracapsular pressure, the latter phenomena partly caused by the vasotoxic effects of the sodium acetrizoate: this was shown by vasodilatation, vascular paralysis, and increased permeability.

5. In comparable doses sodium diatrizoate produced no effect on the renal circulation.

The vascular injuries possibly explain the impairment of renal function observed by earlier investigators after renal angiography, i.e. kidney enlargement, albuminuria and elevated NPN.

Acknowledgement

This investigation was supported by a grant from the Swedish Medical Research Council which is gratefully acknowledged.

SUMMARY

An investigation of the effect upon the renal circulatory system of renal angiography with sodium acetrizoate (Triurol) and sodium diatrizoate (Hypaque) in a material of 14 cats is reported. The marked renal changes which occurred after certain doses of sodium acetrizoate were not observed after comparable doses of sodium diatrizoate.

ZUSAMMENFASSUNG

Eine an 14 Katzen ausgeführte Untersuchung über die Einwirkung der renalen Angiographie mit Natriumacetrizoat (Triurol) und Natriumdiatrizoat (Hypaque) auf den Nierenkreislauf wird berichtet. Die deutlichen Nierenveränderungen, welche nach gewissen Mengen Triurol auftraten, wurden nach vergleichbaren Mengen Hypaque nicht beobachtet.

RÉSUMÉ

L'auteur présente un travail de recherche sur l'effet sur le système circulatoire rénal de l'angiographie rénale avec l'acétrizoate de sodium (Triurol) et le diatrizoate de sodium (Hypaque) sur une série de 14 chats. Les modifications rénales marquées qui se sont produites après certaines doses d'acétrizoate n'ont pas été observées après des doses comparables de diatrizoate de sodium.

difference in the toxicity of sodium acetrizoate and sodium diatrizoate, with the latter less toxic, in agreement with the findings in the present investigation

An attractive explanation of the present results is offered by READ's (1959) interesting observation that large doses of contrast media may cause red cell agglutination He also observed that rapid intravenous injections produced an *increase* of pressure in the pulmonary artery indicating an obstructed blood flow through the lungs The *parallelism between these results in* READ's studies of the pulmonary circulation and the present observations on renal circulatory disturbances is striking

The reports of different disturbances in renal function after renal angiography are abundant, both in animal experiments and investigations in man En largement of the kidney, a sign of renal damage that has not received particular attention, must here be mentioned In a material of 88 cases IDBOHRN (1956) demonstrated kidney enlargement in no less than 10 cases According to this author the sign is more common than elevated NPN (10 of 186 cases) and albuminuria (14 of 172 cases) The kidney enlargement, possibly as well as the graver complications of albuminuria, elevated NPN, and oliguria, can probably be explained by the vascular toxicity of a frequently used contrast medium

The reader should refer to IDBOHRN's article (1956) and to more comprehen sive *monographs, for example of* STIRLING *(1957) and* HELANDER *(1958), for* a more detailed discussion of clinical complications following aortography and renal angiography

The results show, as do those in earlier investigations on the *pharmacologic* effects of contrast media, the importance of the selection of the contrast medium as well as of the dose for arteriographic examinations, it is probable that the majority of the complications can be attributed to damage caused by the drug It would have been interesting from the clinical point of view to have extended the study to include other contrast media as well as the effect of different concentrations of these media on the renal circulatory response described This was not done in the present investigation, however, as its main purpose *was to investigate* the signs of the vasculotoxic effect of sodium acetrizoate This communication thus becomes an addition to the series of publications dealing with the side effects of contrast media in arteriography (LINDGREN & TORNELL *1958*, KAGSTROM, LINDGREN & TORNELL 1958 and 1960, KAGSTROM & LINDGREN 1960)

Conclusions

The renal blood flow *was recorded in cats during* renal *arteriography* with the two contrast media, sodium acetrizoate (Triurol) and sodium diatrizoate (Hyp aque)

1 In single small doses (0 1 to 0 2 ml) sodium acetrizoate produced no change or only a slight increase in the renal blood flow

2 When larger doses of sodium acetrizoate (0 4 to 0 8 ml) were injected a decrease in the blood flow occurred With repeated injections the flow was successively reduced until it finally almost ceased after a total of 2 to 5 ml had been given

3 Postmortem macroscopic examination showed a marked increase in the weight of the injected kidney which was on an average 25 per cent heavier than the contralateral kidney and revealed edematous cyanotic renal tissue

4 The circulatory insufficiency observed was interpreted as secondary to factors including red cell agglutination and obstructed renal capillaries, edema and increased interstitial and intracapsular pressure the latter phenomena partly caused by the vasotoxic effects of the sodium acetrizoate, this was shown by vasodilatation vascular paralysis and increased permeability

5 In comparable doses sodium diatrizoate produced no effect on the renal circulation

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An investigation of the effect upon the renal circulatory system of renal angiography with sodium acetrizoate (Triurol) and sodium diatrizoate (Hypaque) in a material of 14 cats is reported The marked renal changes which occurred after certain doses of sodium acetrizoate were not observed after comparable doses of sodium diatrizoate

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RÉSUMÉ

L auteur présente un travail de recherche sur l effet sur le systeme circulatoire rénal de l angiographie rénale avec l acétrizoate de sodium (Triurol) et le diatrizoate de sodium (Hypaque) sur une série de 14 chats Les modifications rénales marquées qui se sont produites apres certaines doses d acetrizoate n ont pas été observées après des doses comparables de diatrizoate de sodium

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR ÁKOS KOVÁCS) SEMMELWEIS HOSPITAL BUDAPEST, HUNGARY

ROENTGEN PHYSIOLOGY OF THE LARYNX

by

ÁKOS KOVÁCS

The breadth and thickness of the vocal and vestibular folds (the true and false chords) the depth of the ventricle between them and the size of the sac cules of the larynx may be depicted in asymmetric projections of the chords obtained by the aid of the laryngeal 'displacer' described in an earlier paper (KOVÁCS 1960) Changes in these structures during phonation singing swal lowing or blowing may also be demonstrated Before discussing the function of the larynx it may be recalled that the size and shape of the laryngeal carti lages epiglottis ventricle vocal folds and saccules of the larynx present many variations which within certain limits together make up the characteristics of an individual voice

Lateral projection of the larynx The ventricle of the larynx is not always defined in ordinary lateral roentgenograms the patient is usually instructed to hold his breath and during the ensuing forced glottis lock the true and false vocal chords closely approach (Fig 1) so that the ventricle is masked For a demon stration of the ventricle *the patient should* be instructed to exhale and sing a long and deep Oooo when the exposure should be made (Fig 2a) In some cases lateral laryngograms of function may be needed for studying the mobility and dilatatory power of the soft parts of the larynx fixation and rigidity con ti tute valuable diagnostic signs during the initial stages of tumours

An examination of function is performed in the same manner as an examina tion of the hypopharynx Two films are obtained the first while the patient sings a deep soft Oooo and the second during expansion of the larynx which is achieved by telling the patient to blow out and fill the larynx with air while the mouth is shut and the nostrils closed with a nasal clip (Fig 2b)

Submitted for publication 15 February 1961



a b

Fig 1 Valsalva manoeuvre the larynx rises and the trachea hypopharynx and saccules expand the laryngeal ventricle is fully closed and contains no air

Laryngoscopy reveals that the vocal chords do not fully close during phonation During whispering, the arytenoid cartilages slightly separate the vocal chords and air is emitted through a triangular aperture, the employment of more energy will result in weaker vibrations of the chords



a b

Fig 2 a) Phonation of a deep O hypopharynx normal and narrow ventricle appears as a narrow stripe beyond which the arytenoid cartilage tilts somewhat forwards b) Blowing through *a narrow oral aperture* Larynx and hypopharynx (1) together with hyoid bones move upwards the laryngeal ventricle (2) contracts and the arytenoid cartilage (3) moves further forwards

a b

Fig 3 Function of the arytenoid cartilage a) Inhalation the vocal fold (1) is flat transverse section of the arytenoid cartilage (2) b) Phonation longitudinal section of the arytenoid cartilage

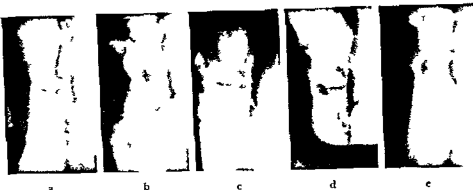


Fig 4 Exam nat n of function of vocal folds in a 17 year-old girl a) During inhalation the vocal l gam nt becomes flat the v ntricle narrow and the aryep glott c fold is arched and slack b) During the phonat n of a deep O the ventricular fold thins th vocal ligament emerges the aryep glottic f ld contracts and the saccules e pand c) Phonation of a h gh pitched I d) With the pharynx and oral cav ty inflated the hypopharynx and saccule expand and the aryep glottic fold contracts e) Val sal a manoeuvre the laryngeal entricle d sappears and the vocal f lds approximate

An examination with the laryngeal displacer will afford better demonstra tion of the chords In most cases both the vocal and the vestibular folds in deep inhalation move outwards and the laryngeal ventricle becomes only a small fossa, during exhalation the size and shape of the vocal folds and the ventricle will be demonstrated only upon phonation The vocal folds of an adult measure 10 to 12 mm in breadth and 6 to 7 mm in thickness in the roentgenograms (Figs 3 and 4)

There is generally a reciprocal effect between the ventricular and the vocal folds During the phonation of a deep sound the ventricular fold is thin and the vocal fold is thick At the phonation of a high sound the process is reversed (Figs 5 and 6)



Fig 5 a) Inhalation b) On phonation of a deep O the entr cular fold is thin the vocal fold th ck c) Duri g the phonat on of a h gh pitched I th vent icular fold th ck and the vocal fold thin



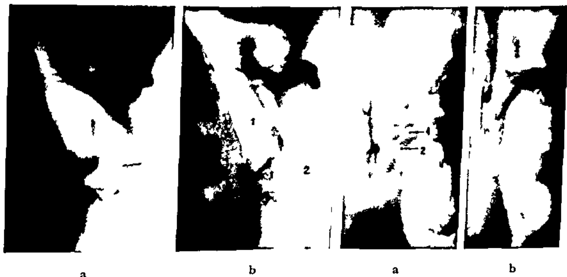
Fig 6 a) Phonation of a h gh note Ve itricular fold thick and vocal fold thin b) Phonation of a deep note ventricular fold thin and vocal fold th ck the larynx has moved downwards c) With the larynx inflated the saccule (1) expands to double its size and reaches far below the glottis Proc transversus (2)



a b

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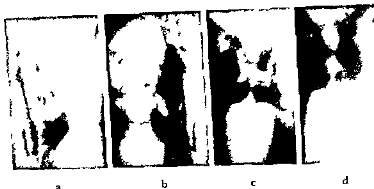


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a b

Fig 3 Function of the arytenoid cartilage a) Inhalation the vocal fold (1) is flat transverse section of the arytenoid cartilage (2) b) Phonation longitudinal section of the arytenoid cartilage



a b c d

Fig 9 Ossified laryngeal cartilages in a man aged 63 During inhalation (a) and (b) the vocal folds do not flatten as in younger subjects On phonation of high and deep sounds (c) and (d) there is little difference in the position of the vocal fold The corniculate cartilages are visible in the second film

Sliding and spiral movements of the arytenoid cartilage with the whole larynx moving upwards could also be demonstrated in lateral roentgenograms with the patient pursing the lips and blowing (Fig 2) These pendular sliding and rotatory movements make possible a gradual adjustment of the glottis

It would appear from displacement films that the level of phonation and possibly its timbre depends to a large extent on the shape of the subglottic area Our films show that during deep phonation the arytenoid cartilage moves to an oblique position and the section of the subglottis takes the shape of a gothic arch (Fig 4b) With a high sound the vocal fold thins and the arytenoid cartilage slides lower and the subglottis becomes semi circular (Fig 4c) It is natural that with the thinning of the vocal fold its mass and consistency will also diminish and consequently its resistance to the outflow of air will be less

Displacement films also showed that the length and tension of the vocal folds are regulated by the cricothyroid muscle As the thyroid and cricoid cartilages approximate the arytenoid cartilage moves backwards like the shorter arm of a lever and stretches the vocal folds (Fig 7)

Ossification of the cricoid cartilage usually appears after middle age but in one case it was found as a fine network in a 30 year old subject

The saccules of the larynx open widely during phonation and may actually expand to twice their normal size Such expansion will be inhibited by malignant infiltration (Fig 6c)

The loudness of speech may be measured in the roentgenogram The difference between a weak and a stronger voice lies in the velocity of the air current and in the size of the air column A wide glottis and laryngeal vestibule are always found in association with a strong voice

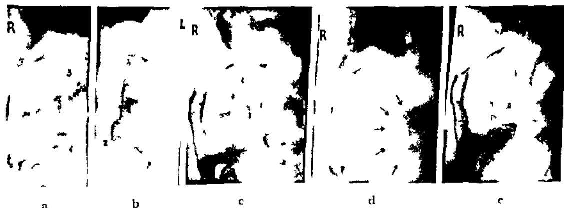
The Valsalva manoeuvre is a valuable complementary method of examination particularly for the initial detection of tumours The manoeuvre may be



a b

Fig 7 Early ossification of the cartilages a) Inhalation b) Movement of the vocal folds *during* phonation The cricoid cartilage (1) rises by about 1 cm in relation to C 7 (2) while the vocal folds (3) fall the small laryngeal ventricle (4) and the vestibular fold become smooth

Examinations were carried out to determine the role played by the arytenoid cartilages, cases being selected in which ossification was commencing to appear in the cartilages (Fig 3) A rotatory motion of each cartilage was seen to occur around an axis through ist attachments, apart from the recognized pendular movements, this motion, which may be demonstrated in displacement films in phonation, completes the approximation of the vocal folds



a b c d e

Fig 8 Paralysis of the right vagus accessory and glossopharyngeal nerves due to syphilis (a) and (b) On inhalation *the right vocal fold* (1) lies inert in the paramedial line while the left *vocal fold* (2) moves out laterally c) During phonation the paralyzed right vocal chord is displaced laterally by the pressure the vocal aperture is open and the left vocal chord now lies in the midline d) Valsalva manoeuvre right side *unaltered the* closely adherent left fold is almost effect the closure e) Exhalation through a pursed mouth with increased thoracic pressure expands the laryngeal ventricle Anomaly of thyroid cartilage which is divided anteriorly (3) R = right L = left

FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF OLLE OLSSON)
UNIVERSITY HOSPITAL OF LUND SWEDEN

THE FIBULA AND ITS RELATIONSHIP TO THE TIBIA AND TALUS IN INJURIES OF THE ANKLE DUE TO FORCED EXTERNAL ROTATION

by

HJALMAR BOLIN

Not very long ago all injuries of the ankle were regarded as dislocations Rupture of the ligaments and fractures of the malleoli began to be described after such conditions had been demonstrated in experimental investigations (DUPUYTREN 1839 MAISONNEUVE 1840 HONIGSCHMIED 1877) The advent of diagnostic roentgenology increased the possibilities of demonstrating bony injuries interest was gradually focused entirely on fractures and the existent knowledge of soft tissue damage appeared to be forced into the background

Attempts to classify the fractures according to the appearance and site resulted in a completely artificial division of uni- bi- and trimalleolar fractures ASHHURST and BROMER (1922) endeavoured to elaborate a classification based on an analysis of a large series of cases grouped according to the supposed mechanisms of the injuries This lead was followed mainly by Scandinavian authors (HANSEN 1942 MAGNUSSON 1944 PALMER 1950 KRISTENSEN 1956) Due particularly to HANSEN s investigation a systematic classification has been devised in which the injuries are grouped according to the nature and thereby to the mechanism of the injury In experimental fractures HANSEN showed a highly significant correlation between the force applied and the consequent injuries to the skeleton and soft tissues (ligaments) Conversely, analysis of the fractures diagnosed offered a possibility of reconstructing the way in which the damage had been caused and which ligaments had been damaged This

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performed during exhalation either by closing the glottis or the mouth and nose, in the first case by compressing the throat the glottis will be closed, and in the second by covering the mouth and pinching the nose in which case the glottis will be open (Figs 1, 2 and 4c) The larynx moves forwards and upwards in both cases, and the subglottis and laryngeal saccules expand If one vocal fold is paralyzed the part of the ventricle on the paralyzed side will dilate (Fig 8) The appearances of the vocal folds are also characteristic The vocal and vestibular folds will merge into a transverse fold and the ventricle will disappear (Fig 8d)

The voice becomes deeper in old age and its compass is likewise reduced due to a general loss of elasticity The characteristic modifications of the vocal folds are consequently not faithfully recorded, for loss of elasticity in the vocal folds impedes lateral displacement even during inhalation (Fig 9)

SUMMARY

Roentgenologic examination of the larynx by means of a special laryngeal displacer permits an observation of function The appearances of the vocal folds the laryngeal ventricle and the laryngeal saccules during ordinary breathing and phonation are described

ZUSAMMENFASSUNG

Die Rontgenuntersuchung mit Hilfe eines Spezialgerates (displacer) gestattet die Darstellung des Larynx und seiner Funktion Das Aussehen der Stimmbander ventriculus et sacculi laryngis wahrend normaler Atmung und Phonation wird beschrieben

RÉSUMÉ

L'examen radiologique du larynx au moyen d'un «déplaceur» *laryngé spécial permet* d'étudier sa fonction L'auteur décrit les images des cordes vocales des ventricules et des saccules du larynx pendant la respiration calme et la phonation

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Fig 2 The articular surface of the fibula and talus

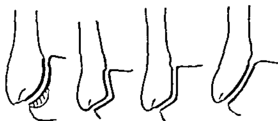


Fig 3 Joint between fibula and talus Varying appearances of the curvature of the articular surfaces in the frontal plane

the lower tapering part facing latero cranially is somewhat convex The bone surfaces of the joint are generally parallel but we have found the thickness of the cartilage particularly in young subjects to be somewhat greater in its apical portion The curvature of the articular surface in the frontal plane varies widely (Fig 3) Since the two articular surfaces of the injured ankle are often no longer parallel they must be examined separately This is facilitated by the fact that the cortex under the cartilage can be demonstrated in suitable projections this applying in particular in the case of the fibula In addition slight modifications in projection will show differences in the outlines of the articular surfaces which will facilitate the evaluation of the articular surface of the talus (Fig 4) It should be mentioned that this joint has more than only a guiding function and normally, bears part of the weight of the body placed on the talus during standing and walking

The two opposing surfaces of the fibula and tibia at the syndesmosis have been the subject of many investigations These surfaces are normally neither flat nor parallel They have no cortex and they cannot be projected free which explains the difficulties encountered in the evaluation of la ligne claire i e the width of the syndesmosis Other approaches must therefore be tried, and we have found that the roentgenologist is on much firmer ground if he judges the state of the mortise of the ankle by a consideration of the articular surfaces

Nomenclature Knowledge of the anatomic features described are obviously necessary for the evaluation of fractures, particularly external rotation fractures These occur on forced external rotation of the foot or more commonly by internal rotation of the lower leg with the foot fixed The type of injury will differ with the position of the foot i e whether it is supinated (adducted) or pronated (abducted) at the time of the forced rotation (HANSEN) There is still some confusion concerning the nomenclature although the authors agree in principle

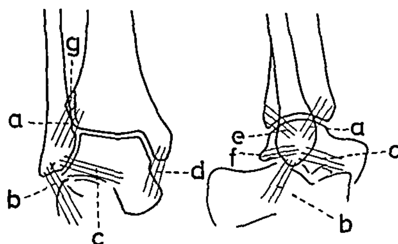


Fig. 1. Ligaments.
a) Anterior tibiofibular
b) Calcaneofibular
c) Anterior talofibular
d) Deltoid
e) Posterior tibiofibular
f) Posterior talofibular
g) Interosseous

aetiologic classification of indirect ankle injuries has been generally accepted by those interested in this field, but since it is somewhat complicated it has not been as widely accepted as it deserves.

The primary results of the treatment of a fracture of the ankle with little displacement are, as a rule, good and the risk of pseudoarthrosis, for example, is negligible. Control examinations have, however, shown a considerable frequency of late symptoms attributable to changes of the arthrosis deformans type. Thus MAGNUSSON found that such changes are common after injuries caused by forced external rotation. In a series of ankle fractures of this type (211 cases), not treated surgically, symptoms were noted in 30 to 35 per cent and arthrosis deformans in 30 to 100 per cent, according to the severity of the injury. This investigation and other data in the literature together with personal experience have convinced us that external rotation injuries require a refined diagnosis and careful treatment.

In practically all ankle injuries caused by indirect violence the damage to the fibula and its ligamentous attachments is most important from the view-point of classification and treatment.

Anatomy. The fibula is connected to the tibia by the anterior tibiofibular ligament, the interosseous ligament and the posterior tibiofibular ligament with attachments to the anterior tubercle, the fibular incisura and the posterior tubercle of the tibia, respectively (Fig. 1). Both malleoli are also connected by ligaments to the talus both anteriorly and posteriorly and with the calcaneum.

The joint between the fibula and the talus is of particular interest. The articular surface of the fibula is that of an inverted triangle and lies in the sagittal plane (Fig. 2). The lateral articular surface of the talus is wedge-shaped with its apex likewise being directed downwards. The upper and larger portion of this articular surface is flattened in the sagittal plane while

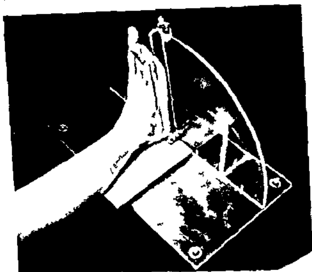


Fig 5 Device used in the roentgen examination of an ankle injury

The pronation eversion type may also be divided into four stages

I Transverse avulsion fracture of the medial malleolus or rupture of the deltoid ligament

II (I) + avulsion of the anterior tibiofibular ligament and antero posterior rupture of the interosseous ligament

III (II) + short spiral fracture of the fibula above the syndesmosis (sometimes high up near the knee joint)

IV (III) + fracture of the posterior tibial margin (posterior tubercle) often with luxation

The line of injury follows the direction of the violence medial malleolus anterior tibiofibular and interosseus ligaments fibula posterior tubercle

In both types of fracture the damage to the fibula and its ligaments are much more serious than what might be expected from the roentgen appearance This is discussed more in detail in the following two examples

1 Roentgen examination shows the usual oblique fibular fracture at the level of the syndesmosis (supination eversion fracture stage II) as the only injury This means that the anterior tibiofibular ligament has been avulsed completely and the fibular fragment can rotate outwards and is held only by the intact posterior ligament and the collateral ligaments The ankle mortise no longer has its lateral support even if the fibular fragment is not displaced On cessation of the forced outward rotation the fibular fragment springs back but as a rule such spontaneous reduction is not entirely satisfactory There is often a slight dorsolateral displacement which is relatively easily demonstrated A persistent outward rotation of the lower fibular fragment is common and may be considerable the roentgenologist should

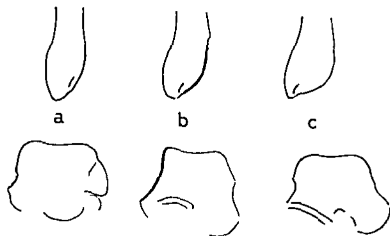


Fig. 4. Variations in appearance of the fibula and talus with different positions of the foot. a) 15° too little inward rotation. b) correct position. c) 15° too much inward rotation.

The former type is called either a supination external rotation fracture (with a frequency of 65 %) or a supination eversion fracture (HANSEN), or a supination abduction fracture (PALMER).

The latter type is by analogy called either a pronation external rotation fracture (with a frequency of 10 %), or a pronation eversion fracture (HANSEN), or a pronation abduction fracture (PALMER).

Other types of indirect ankle fractures are briefly: supination (adduction) injury (frequency about 15 %), pronation (abduction) injury (frequency about 5 %), axial compression injury and dorsal flexion and plantar flexion injuries (frequency about 5 %).

It is clear from the figures given above that supination eversion fractures are most common and represent more than half and, together with pronation eversion injuries, three fourths of all ankle fractures. The nomenclature suggested by HANSEN is subsequently used.

Grading of fractures. Supination eversion fractures may be divided into four stages:

I. Avulsion of the anterior tibiofibular ligament with or without detachment of bone.

II. (I) + oblique spiral fracture of the fibula with the anterior margin at the level of the talo crural joint and running obliquely upwards posteriorly.

III. (II) + fracture of the posterior tibial margin (avulsion of fragment from the posterior tibial tubercle).

IV. (III) + transverse avulsion fracture through the medial malleolus or rupture of the deltoid ligament. The foot is sometimes dislocated backwards. In the memorization of these stages it is useful to bear in mind that the line of injury is determined by the direction of the violence: anterior tibiofibular ligament, fibula, posterior tubercle, medial malleolus.

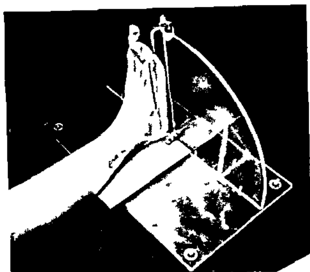


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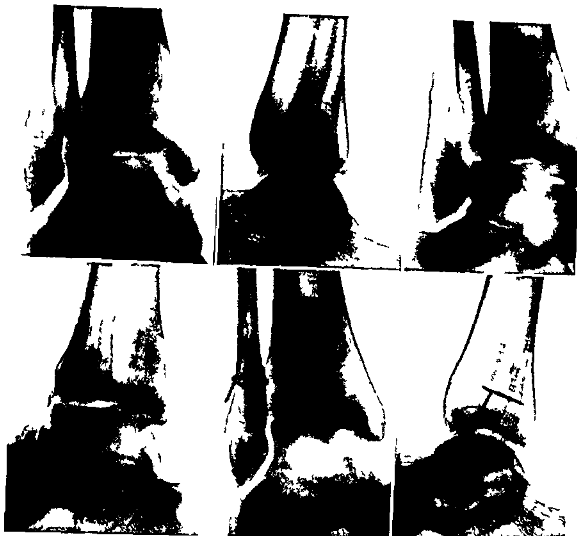


Fig. 6. Supination eversion fracture stage IV lateral displacement of the talus and fibular fragment. The tibiofibular and deltoid ligaments were sutured and a wire was laid around the fibula. Excellent position.

therefore be on the watch for any such rotation. Finally it should be stressed that the fibular fragment may also be displaced in a proximal direction with incongruence of the joint as a consequence.

II. On roentgen examination of the ankle only a transverse avulsion fracture of the medial malleolus is found. This may actually mean a severe pronation eversion injury and indicates examination of the entire fibula. In stage II of this type of injury the fibula has been rotated so much that the syndesmosis has been damaged and especially after a high fibular fracture (stage III) there is a risk of the loose distal fragment remaining in malposition (external rotation, dorso lateral displacement or proximal displacement). It should be observed that on outward rotation only the syndesmosis may be slightly widened even if it appears to be of normal width in the roentgenogram. The width of the syndesmosis should be judged with knowledge of the type of fracture. In this connection it must be stressed that a widening of the syndesmosis is sometimes detected by displacement at the internal malleolus due to the outward rotation of the talus together with the fibula.



Fig 7 Supination eversion fracture stage IV Fibular fragment rotated outwardly and displaced laterally dorsally and proximally After screwing the displacement persists essentially unchanged

Examination technique

It has been claimed that considerable malposition of the fibula may be present without being demonstrable in the roentgenogram This has been pointed out for example by HANSEN who on experimental outward rotation of the foot found a discrepancy between the results of roentgen examinations and autopsy dissections Such a conclusion cannot be accepted because it is founded on an inadequate examination technique

Since it is necessary not only to diagnose fractures but also to conclude whether the ligaments have been damaged and to demonstrate any malposition of the fragments investigation of an ankle injury places exacting demands on the examination technique The examination should include a frontal view with the beam directed in the plane formed by the joint between the fibula and the talus The practical problem is to find this projection We use a simple aid consisting of a semi circular disk placed vertically and against



Fig 8 Pronation-eversion fracture stage IV (There is also a fracture of the middle of the fibula) Total rupture of the deltoid ligament and of the ligaments between the fibula and the tibia was confirmed at operation The fibula is rotated outwardly and displaced proximally

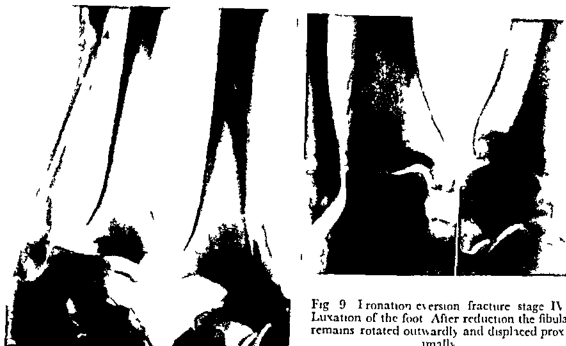


Fig 9 Pronation eversion fracture stage IV Luxation of the foot After reduction the fibula remains rotated outwardly and displaced proximally

which the foot (heel and fore foot) is supported The lateral side of the foot is pressed against a wing, which is placed at the desired angle (Fig 5) As a rule, a good frontal view may be obtained with a 10° inward rotation of the lateral margin of the foot Otherwise the first film will usually indicate how large the angle should be, the suitable angle lies between 0 and 20° inward rotation Lateral films are taken at 85° outward rotation At the first examination films are also obtained in two oblique projections of 35° inward and 55° outward rotation These films are usually sufficient to demonstrate the relationships of the medial malleolus as well The examination must sometimes be supplemented by a frontal film in which the foot is outwardly rotated 10° more than in the usual projection

If it is a question of a recent fracture with considerable displacement, such precision in the projection is not necessary Still more important is the accuracy of the technique when the fracture is reduced and in plaster The plaster should be provided with a straight lateral edge to enable adjustment of the apparatus, this being necessary not only to judge the reduction but also for comparison with later films

Results

It is possible to reveal small displacements and rotations with the method described Malposition has been demonstrated even after apparently satisfactory reduction, which has prompted our orthopedic colleagues to try new

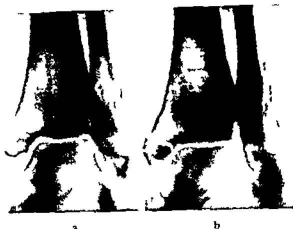


Fig 10 Two frontal views of the same case of a supination-eversion fracture stage IV The lateral articular surface of the talus is well seen in (a) The foot is rotated inwards a further 20 in (b) and the joint surface of the fibula is better seen

methods promising better results Figs 6 to 10 show cases with different types of treatment

Roentgen examination of ankle joint injuries should aim not only at demonstrating fractures but also at classifying them according to type and stage Technically satisfactory examinations will also show which ligaments are damaged A careful search should be made for even slight malposition, this requires the examination of the articular surfaces of the ankle mortise Demonstration of such malposition facilitates correct reduction and immobilization and improves the end results i e post traumatic changes will be less common and less severe

SUMMARY

Outward rotation injuries of the ankle joint fall into two aetiologic types representing three fourths of all fractures of the ankle joint and characterized by serious damage to the mortise as a whole An adequate examination requires careful evaluation of the articular surfaces A simple apparatus is described to facilitate a refined diagnosis which is necessary for correct reduction

ZUSAMMENFASSUNG

Eversionsschaden des Fussgelenkes können in zwei ätiologischen Typen eingeteilt werden welche drei Viertel aller Frakturen des Fussgelenkes umfassen und durch ernste Schädigung der Gabelung als gesamt charakterisiert sind Eine adäquate Untersuchung erfordert sorgfältige Beurteilung der Gelenkoberfläche Ein einfacher Apparat wird beschrieben welcher die verfeinerte Diagnostik erleichtert die für eine korrekte Reduktion notwendig ist

RÉSUMÉ

Les traumatismes de la cheville par rotation externe se divisent en deux types étiologiques représentant les trois quarts de toutes les fractures de la cheville et se caractérisent par des lésions graves de la mortaise dans son ensemble Il est nécessaire de faire une étude soigneuse de l état des surfaces articulaires L auteur décrit un appareil simple qui facilite le diagnostic de précision qui est nécessaire pour une réduction correcte



Fig 9 Pronation eversion fracture stage IV Luxation of the foot After reduction the fibula remains rotated outwardly and displaced proximally

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It is possible to reveal small displacements and rotations with the method described Malposition *has been demonstrated even after apparently satisfactory* reduction, which has prompted our orthopedic colleagues to try new

FROM THE DEPARTMENT OF SURGERY (DIRECTOR PROF N OBEL) ROYAL VETERINARY COLLEGE, STOCKHOLM, SWEDEN

EFFECT ON THE SPINAL CORD OF SUBARACHNOID INJECTION OF WATER-SOLUBLE CONTRAST MEDIUM

An experimental study in dogs

by

B FUNKQUIST and N OBEL

It is a well established fact that lumbar myelography with a water soluble contrast medium may give rise to alarming states of collapse (LINDBLOM 1947, KNUTSSON 1950 PANTER 1953 GROTE 1955, KOLSTAD 1959) On the other hand, judging by the available literature little attention seems to have been focused on the possibility of long standing functional disturbances and of morphologic changes in the spinal cord after subarachnoid injection of hypertonic solutions in general and of water soluble contrast media in particular

In earlier experiments on the effect on the blood pressure of subarachnoid injection of a water soluble contrast medium (FUNKQUIST & OBEL 1960), we had an opportunity of studying some of the experimental animals after they had recovered from the anaesthetic In the first few experimental series, no signs of functional disturbances of the nervous system could be detected after the lumbar subarachnoid injection of 0 5 ml/kg bodyweight of Kontrast U© 20 % with the addition of Xylocaine© in varying concentrations of up to 0 5 %

We subsequently used the same preparation for diagnostic purposes in dogs with signs of spinal cord compression the experimental conditions then being somewhat modified Lengthy paresis of the hind legs appeared in two of these dogs after subarachnoid injection of contrast medium mixed with Xylocaine Shortly before it one of the dogs had been given an i v injection of hypotonic saline to stimulate the production of cerebrospinal fluid and thus facilitate a check on the position of the lumbar needle In the other dog we intended to

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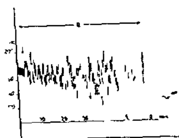


Fig 1 Blood pressure in femoral artery after lumbar subarachnoid injection (A) of Kontrast U 20 containing 5 mg/ml Xylocaine hydrochloride Hypotensive effect of the subarachnoid injection counteracted by repeated injections (B) of noradrenaline

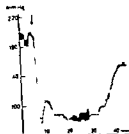


Fig 2 Blood pressure in femoral artery after lumbar subarachnoid injection (A) of Kontrast U 20 containing 5 mg/ml Xylocaine hydrochloride

In all the experimental groups the amount of contrast medium injected by the subarachnoid route was 0 5 ml/kg bodyweight and the number of experimental animals was 3 in each one of these groups In other respects the experimental conditions were varied as follows

A Contrast medium injected in the course of about 15 sec Any tendency to a fall in blood pressure was counteracted by the continuous i v injection (or repeated intravenous injections) of noradrenaline (0 8 to 2 0 μg/kg bodyweight per minute during 40 to 60 minutes) The rate of infusion was adapted so that blood pressure deviated as little as possible from the initial level i e before the injection of contrast medium (Fig 1)

B Contrast medium injected in the course of 180 sec Other conditions as in (A)

C Contrast medium injected in the course of about 15 sec The blood pressure (Fig 2) was not corrected but was allowed to fall to a level dependent on the effect of the mixture of contrast medium and Xylocaine (FUNKQUIST & OBEL 1960) After injection the check on the blood pressure was continued for so long (at least 40 min) that the animal s own regulatory mechanism was able to keep it above 120 mm Hg

D Contrast medium injected in the course of 180 sec Blood pressure uncorrected and checked as in (C)

E Contrast medium injected in the course of 15 sec The blood pressure was further reduced — in addition to the fall dependent on injection of contrast medium and Xylocaine — by withdrawal of blood through a polythene catheter (PE 260 Clay Adams New York) introduced into the aorta via the carotid artery By repeated withdrawals of blood alternating with small intra arterial or i v transfusions of citrated blood (25 to 50 ml each time) the blood pressure was kept in the vicinity of 60 mm Hg for about 20 min (Fig 3) The blood volume was then restored and the blood pressure raised to a level close to the initial value by the i v injection of noradrenaline it was maintained at this level by continuous infusion or repeated intravenous injections of the preparation The check on the blood pressure and its correction were continued for so long after the period of hypotension (for about 40 min) that the animal s own regulatory mechanism was able to keep the pressure at the initial level or slightly below it On no occasion during the experiments did the difference between the volume of blood withdrawn and that transfused exceed 150 ml The dose of noradrenaline was 0 4 to 1 2 μg/kg bodyweight per minute during 30 to 35 minutes

follow the spreading of the contrast medium in the subarachnoid space by means of fluoroscopy The solution was therefore injected more slowly than in the previous experiments, i e in the course of several minutes, instead of within 10 to 15 sec Moreover, a considerable fall in blood pressure occurred in the second dog during the first few minutes after injection of the mixture of contrast medium and Xylocaine, and necessitated the i v injection of nor adrenaline

This experience seemed to justify a more detailed analysis of the effect of subarachnoid injection of water-soluble contrast medium on the spinal cord In view of the aforegoing primary observations, we devoted the first part of the study to the influence on damage by contrast medium of some conditions that may, in fact, apply in the clinical use of water soluble contrast medium for thoracolumbar myelography These consist of variations in the arterial blood pressure in connexion with injection of the medium, and of variations in the rate at which the subarachnoid injection is made In the second part of the study we have tried to analyze the pathogenetic mechanism of the damage Our main interest has then been concentrated on the question of whether the damage is dependent chiefly on osmotic factors or whether it is also necessary to envisage a more specific toxic effect on the neural elements of the spinal cord, or on its blood vessels

I Attempts to provoke spinal cord damage by variations in rate of injection of contrast medium and in blood pressure after injection

Healthy dogs aged 6 months to 2 years and weighing 7 to 21 kg were used for the experiments They were anaesthetized by i v injection of Intraval©, after which lumbar puncture of the subarachnoid space was performed (FUNKQUIST 1960) The dogs were then placed on the right side, with their forequarters elevated about 30° Anaesthesia was maintained by a mixture of nitrous oxide and oxygen (4 1) Complete muscle relaxation was induced and maintained by the repeated i v injection of succinylcholine iodide (Celocurin iodide©) in doses of 0 5 mg/kg After intubation, artificial respiration was given with a 'Pulmomat' (Dräger) The spinal fluid was allowed to run through the lumbar needle until, before the injection of contrast medium, the flow had ceased or had diminished to a constant rate of a few drops per minute

The contrast medium used was Kontrast U® 20 % with the addition of 0 5 mg/ml Xylocaine hydrochloride The arterial blood pressure was recorded throughout the experiment by the method of HANSSON & OBEL (1958) In some experimental groups the fall in blood pressure was counteracted by continuous i v infusion of a noradrenaline solution containing 20 μg/ml noradrenaline bitartrate In the relevant cases the dogs were killed by the rapid i v injection of pentobarbital sodium (Mebumalnatrium©) 6 % in an approximate dose of 6 cg/kg bodyweight

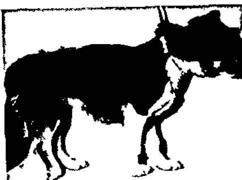


Fig 4



Fig 5

Fig 4 and 5 Dogs 24 hours after lumbar subarachnoid injection of Kontrast U with Xylocaine After injection a 20 min period of severe hypotension In fig 4 mild paresis of right hind leg (grade I) in fig 5 moderate paresis of right hind leg (grade II)

III Severe paresis to paralysis of the right hind leg Paresis of varying degree of the left hind leg (Cf Fig 8)

The functional disturbances generally decreased successively during the observation period (1 to 6 days) The disturbances listed in the Table (pp 454—455) refer to the condition 24 hours after injection of contrast medium

The morphologic changes in the spinal cord observed in some of the experimental groups were in the nature of oedema localized to the white matter generally of a markedly focal nature (Figs 6 and 7) The largest foci were usually localized to the right side laterally or dorso and ventrolaterally,



a b

Fig 6 a) Cross-section of the spinal cord (L4) 3 days after lumbar subarachnoid injection of Kontrast U 20 with Xylocaine Injection followed by a 20 min period of severe hypotension (I—E in text) Oedematous focus in the white matter of the spinal cord laterally on right side Haematoxylin and eosin × 50 b) Detail of (a) × 150

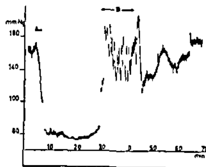


Fig 3 Blood pressure in femoral artery after lumbar subarachnoid injection (A) of Kontrast U 20 % mixed with Xylocaine Hypotensive effect of the injection accentuated by withdrawal of blood After about 20 min hypotension (blood pressure kept at around 60 mm Hg) the blood pressure was restored to approximately the initial level by blood transfusion and repeated intravenous injections (B) of noradrenaline

F Contrast medium injected in the course of 180 sec Other conditions as in (E) The dose of noradrenaline was 0 4 to 1 2 μg/kg bodyweight per minute during 10 to 20 minutes

G Ringer s solution containing 5 mg/ml Xylocaine hydrochloride (1 vol commercial Xylocaine solution 2 % + 3 vol Ringer s solution) injected into the subarachnoid space in the course of 15 sec Other conditions as in (E) The dose of noradrenaline necessary for maintenance of normal blood pressure after the period of hypotension was 0 6 to 1 2 μg/kg body weight per minute during 30 to 40 minutes

After the subarachnoid injection the dogs in all the groups were allowed to lie with the forequarters elevated for about 60 minutes They were then placed in the horizontal position, and left until they made spontaneous attempts to get up The dogs were observed for neurologic symptoms and signs for 1 to 6 days, after which they were killed The vertebral canal was opened immediately after death, and specimens taken from the spinal cord at the level of C7, Th4, Th10 and Th13, as well as L1, L2, L3, L4, L5 and L6 The specimens were fixed in 10 % formalin dissolved in physiologic saline, embedded in paraffin, and cut transversely into sections 7 to 8 μ thick The sections were stained with *haematoxylin* and eosin, *and in some cases also with luxol fast* blue and Holmes silver nitrate according to Pickett and Margolys

Results Functional and morphologic signs of spinal cord damage were observed in some of the experimental groups Both were consistently more marked on the side (the right) on which the dog had been lying during and after injection

The degree of functional *spinal cord damage could* be classified as follows on the basis of the loss of motor function (The descriptions refer to certain typical combinations, transitional forms obviously being common)

I Mild to moderate paresis of the right hind leg The dog could advance the leg completely or partly at a walking pace, but dragged the dorsal side of the paw on the ground (Fig 4)

II Severe paresis of the right hind leg The dog could not advance the leg, which dragged stiffly behind it, *with the dorsal side of the paw* on the ground (Fig 5)

Table (cont)

Experiment according to headings in text	Functional disturbances				Morphologic changes			
	Grade III	Grade II	Grade I	0	Grade III	Grade II	Grade I	0
I A				3			1	2
B				3				3
C				3			1	2
D				3			1	2
E	1		1	1	1	1	1	
F	1	1		1	2		1	
I G				3				3
II A				3		1	2	
B			1	2			2	1
C	3				3			
II A								2
B		1	1			1	1	
C	1		1		1			1

In these cases the changes in the axis cylinders were restricted to moderate swelling In cases with severe damage to the spinal cord the foci were larger they were sometimes confluent and often displayed a central area of necrosis (Fig 7 Cf Figs 9 and 10) The axis cylinders were much swollen (Cf Fig 11) at the margins of the necrotic areas Within the necrotic areas there was a complete disintegration of the myelin sheaths and the axis cylinders were broken up into fragments (Cf Fig 10) The severest lesions were often localized to a region at the level of L3 – L5 with a successive decrease in severity in the cranial and caudal directions The frequency of necrosis within the foci and the extent of the lesions often showed the following correlation in the animals with the most marked tendency to central necrosis in the foci the anterior margin of the damaged part of the spinal cord also lay furthest cranially

Some proliferation of the glia was present in addition to the changes described above in certain dogs killed 4 to 6 days after the subarachnoid injection The length of the interval between the injection and killing of the animal seemed otherwise to have fairly little influence on the histopathologic changes

The spinal leptomeninges in the lumbar region exhibited an inflammatory reaction of varying degree (mild to moderate) in most cases No correlation seemed to exist between the degree of inflammatory reaction and the degree of damage to the spinal cord

Table

Relation between experimental conditions and spinal cord damage in lumbar subarachnoid injection of hypertonic solutions

Summary of experimental conditions	Experiment according to headings in text	Mean blood pressure first 20 min after injection * (mm Hg)	Duration of injection (sec)	Number of dogs
Subarachnoid injection of Kontrast U 20 with Xylocaine 0 5 Variation in duration of injection and in blood pressure after the injection	I A	180 (180)	15	3
	B	185 (180)	180	3
	C	100 (185)	15	3
	D	85 (160)	180	3
	E	60 (165)	15	3
	F	65 (150)	180	3
Subarachnoid injection of Ringer s solution with Xylocaine 0 5 Provoked fall in blood pressure after the injection	I C	60 (125)	15	3
Subarachnoid injection of Kontrast U 20 with Xylocaine 0 1 *No pretreatment (A) previous i v injection of physiol saline (B) and hypotonic saline (C)*	II_1 A	145 (160)	15	3
	B	140 (160)	15	3
	C	125 (155)	15	3
Subarachnoid injection of saline 5 1 (isotonic with Kontrast U 20) with Xylocaine 0 5 Variation in blood pressure after the injection	II_2 A	165 (155)	15	2
	B	85 (175)	15	2
	C	60 (165)	15	2

* *The mean value for the single animal was obtained by planimetric calculation* The value in the table represents the mean for all the animals in the relevant group The bracketed figures denote the mean of the blood pressure values immediately before injection of contrast medium

respectively As a rule a narrow strip of intact tissue was visible between the focus and the pia In the cases with mild changes (Fig 6), *there was only a* certain porosity of the tissue in the foci, apparently caused by an increased fluid content, partly within the myelin sheaths, partly between the nerve fibres



a b

Fig 7 a) Cross section of the spinal cord (L5) 4 days after lumbar subarachnoid injection of Kontrast U 20 , with Xylocaine Experimental conditions otherwise as in fig 6 Oedematous focus with central necrosis ventrolaterally in the white matter of the cord Haematoxylin and eosin × 50 b) Detail of (a) × 150

Table (cont)

Experiment according to headings in text	Functional disturbances				Morphologic changes			
	Grade III	Grade II	Grade I	0	Grade III	Grade II	Grade I	0
I A				3			1	2
B				3				3
C				3			1	2
D				3			1	2
E	1		1	1	1	1	1	
F	1	1		1	2		1	
I G				3				3
II A				3		1	2	
B			1	2			2	1
C	3				3			
II A				2				2
B		1	1			1	1	
C	1		1		1			1

In these cases the changes in the axis cylinders were restricted to moderate swelling In cases with severe damage to the spinal cord the foci were larger they were sometimes confluent and often displayed a central area of necrosis (Fig 7 Cf Figs 9 and 10) The axis cylinders were much swollen (Cf Fig 11) at the margins of the necrotic areas Within the necrotic areas there was a complete disintegration of the myelin sheaths and the axis cylinders were broken up into fragments (Cf Fig 10) The severest lesions were often localized to a region at the level of L3 — L5 with a successive decrease in severity in the cranial and caudal directions The frequency of necrosis within the foci and the extent of the lesions often showed the following correlation in the animals with the most marked tendency to central necrosis in the foci the anterior margin of the damaged part of the spinal cord also lay furthest cranially

Some proliferation of the glia was present in addition to the changes described above in certain dogs killed 4 to 6 days after the subarachnoid injection The length of the interval between the injection and killing of the animal seemed otherwise to have fairly little influence on the histopathologic changes

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The morphologic changes in the spinal cord were graded as follows
I — A few oedematous foci in the vicinity of the puncture site (L4 — L5),
II — Several oedematous foci spread over the lumbar region,
III — Oedematous foci in both the lumbar and thoracic regions

It is evident from the table that in the dogs whose blood pressure was normal or moderately reduced after injection of contrast medium the spinal functional disturbances were not of such degree that they could be observed on ordinary inspection Some of these animals, however, displayed morphologic changes of grade I When the blood pressure was greatly reduced after injection (to about 60 mm Hg), functional and morphologic signs of severe spinal cord damage were, on the contrary, present in most animals The variations in the rate of injection did not have any apparent effect on either the incidence of spinal cord damage or its nature The dogs given a subarachnoid injection of Xylocaine 0 5 % in Ringer s solution exhibited neither functional nor morphologic signs of spinal cord damage after severe hypotension

II Attempts to analyze the pathogenetic mechanism of spinal cord damage due to contrast medium

Unless otherwise stated, the experimental conditions with respect to anaesthesia and other factors were the same as those listed under heading (I)

1 Effect on the spinal cord of subarachnoid injection of contrast medium after previous i v injection of hypotonic saline

Lumbar puncture was performed on 9 dogs, aged 6 months to 2 years and weighing 8 to 23 kg They were placed with the forequarters elevated 30°, and the spinal fluid was allowed to run through the puncture needle until the flow had ceased, or had diminished to a constant rate of a few drops per minute Kontrast U 20 %, with the addition of 1 mg/ml Xylocaine hydrochloride, was injected through the lumbar needle in a dose of 0 5 ml/kg bodyweight In 3 of the dogs (group A) injection of contrast medium was performed without any special pretreatment Three of the dogs (group B) received, before injection of the contrast medium, an i v injection of 10 ml/kg bodyweight saline 0 9 % in the course of 2 to 4 minutes Three of them (group C) were pretreated by i v injection (at the same rate) of 10 ml/kg bodyweight saline 0 3 % In the pretreated dogs, the interval between the end of the i v injection and injection of the contrast medium was about 4 minutes

The dogs were left with the forequarters elevated for about 1 hour, after which they were placed in the horizontal position The experimental conditions were the same, in relevant details, as those described under (I) The dogs were



F g 8 Dog 24 hours after lumbar subarachno d injec t on of Kontrast U 20 w th Xyloca ne Pretreatment by i v injection of hypotonic sal ne Paralys s of right h nd leg and severe pares s of left hind leg (grade III)

t under observation for 1 to 4 days and then killed Specimens of the spinal d were taken at the level of C7, Th4 Th10 and Th13 as well as L1, L2 L3, L5 and L6 and examined histologically

Results At examination 24 hours after injection of contrast medium (see ble) the 3 dogs given a previous i v injection of saline 0 3 % had paralysis severe paresis of the right hind leg and severe (Fig 8) or moderate paresis the other leg (grade III) In the group which had been pretreated by the injection of isotonic saline one dog had a mild paresis (grade I) of the right d leg The other 2 dogs in this group walked normally No signs of disturb- es in spinal cord function were present in the controls which had not been en any previous fluid injection

Histologic examination (see Table) of specimens of the spinal cord from dogs treated by the i v injection of hypotonic saline showed lesions (Figs 9 10 d 11) of the same type as those observed in series (I) E and F, i e several dematous foci in the white matter of the cord in the lumbar and thoracic gions with central necrosis in many of the oedematous areas (grade III) the other groups the morphologic changes if present were restricted to lumbar region (grades I and II)

? *Effect on the spinal cord of subarachnoid injection of hypertonic saline*

Since the osmotic pres ure of Kontrast U 20 % had been calculated to cor pond to that of a 5 1 % solution of saline the experiments listed under (I), C and E were repeated but substituting saline 5 1 % (with Xylocaine 0 5 %)

The morphologic changes in the spinal cord were graded as follows
I — A few oedematous foci in the vicinity of the puncture site (L4 — L5),
II — Several oedematous foci spread over the lumbar region,
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It is evident from the table that in the dogs whose blood pressure was normal or moderately reduced after injection of contrast medium the spinal functional disturbances were not of such degree that they could be observed on ordinary inspection Some of these animals, however, displayed morphologic changes of grade I When the blood pressure was greatly reduced after injection (to about 60 mm Hg), functional and morphologic signs of severe spinal cord damage were, on the contrary, present in most animals The variations in the rate of injection did not have any apparent effect on either the incidence of spinal cord damage or its nature The dogs given a subarachnoid injection of Xylocaine 0 5 % in Ringer's solution exhibited neither functional nor morphologic signs of spinal cord damage after severe hypotension

II Attempts to analyze the pathogenetic mechanism of spinal cord damage due to contrast medium

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The dogs were left with the forequarters elevated for about 1 hour, after which they were placed in the horizontal position The experimental conditions were the same, in relevant details, as those described under (I) The dogs were



Fig 8 Dog 24 hours after lumbar subarachnoid injection of Kontrast U 20 with Xylocaine Pretreatment by i v injection of hypotonic saline Paralysis of right hind leg and severe paresis of left hind leg (grade III)

kept under observation for 1 to 4 days and then killed Specimens of the spinal cord were taken at the level of C7, Th4 Th10 and Th13 as well as L1 L2, L3, L4 L5 and L6 and examined histologically

Results At examination 24 hours after injection of contrast medium (see Table) the 3 dogs given a previous i v injection of saline 0 3 % had paralysis or severe paresis of the right hind leg and severe (Fig 8) or moderate paresis of the other leg (grade III) In the group which had been pretreated by the i v injection of isotonic saline one dog had a mild paresis (grade I) of the right hind leg The other 2 dogs in this group walked normally No signs of disturbances in spinal cord function were present in the controls which had not been given any previous fluid injection

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2 *Effect on the spinal cord of subarachnoid injection of hypertonic saline*

Since the osmotic pressure of Kontrast U 20 % had been calculated to correspond to that of a 5 1 % solution of saline, the experiments listed under (I) A C and E were repeated, but substituting saline 5 1 % (with Xylocaine 0 5 %)

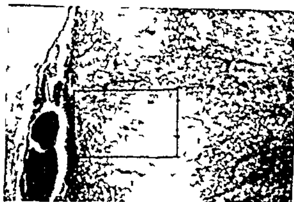


Fig 9 Cross section of spinal cord (Th10) 4 days after lumbar subarachnoid injection of Kontrast U 20 % with Xylocaine Pretreatment by i v injection of hypotonic saline before injection of contrast medium Normal blood pressure during experiments Confluent oedematous foci with central necrosis laterally in the white matter Haematoxylin and eosin × 50

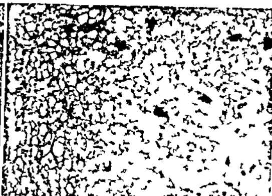


Fig 10 Cross section of the spinal cord (Th10) 4 days after lumbar subarachnoid injection of Kontrast U 20 % with Xylocaine The experimental conditions were the same as in fig 9 Part of oedematous focus with central necrosis (to the right) Haematoxylin and eosin × 150

for the contrast medium Six dogs in all were used for the experiment, their ages were from one to two years and their weight ranged from 8 to 18 kg The animals were divided into 3 groups with two animals in each In the first group (A), corresponding to I A, the tendency to a fall in blood pressure was counteracted by an injection of noradrenaline In the second (B) and third (C) groups, corresponding to I C and I E, a moderate and severe fall, respectively, in arterial blood pressure was provoked during and after the subarachnoid injection To check the position of the needle tip, 0 1 to 0 2 ml lipiodol was injected through the lumbar needle directly after the injection of saline

Results The 2 dogs whose blood pressure during injection was close to the initial level, showed neither functional disturbances nor morphologic changes in the spinal cord The other 4 dogs whose blood pressure had been moderately and greatly reduced after the injection exhibited varying degrees of functional disturbances and morphologic lesions described in the account of the results of subarachnoid injection of contrast medium (see the table, pp 454—455 and Fig 12)

3 *Effect on the blood spinal cord barrier of subarachnoid injection of Kontrast U in varying concentration and of hypertonic saline*

Lumbar and suboccipital puncture were performed on 7 dogs, aged 5 months to 2 years and weighing 8 to 20 kg The hindquarters of the dogs were elevated about 30°, and the spinal fluid allowed to run freely through the suboccipital needle When the flow of spinal fluid had ceased, or was reduced to a few drops per minute, the forequarters of the dogs were raised about 30° Injection was



Fig 11 Cross-section of the spinal cord (T13) 24 hours after lumbar subarachnoid injection of Kontrast U 20 Experimental conditions as in fig 9 Part of oedematous focus near its necrotic centre The axis cylinders are greatly swollen Haematoxylin and eosin × 500

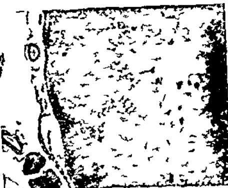


Fig 12 Cross-section of spinal cord (L4) 24 hours after lumbar subarachnoid injection of saline 5 1 with Xylocaine Injection followed by a 20 min period of severe hypotension Sharply defined oedematous focus with central necrosis ventrolaterally in the white matter Haematoxylin and eosin × 50

then made through the lumbar needle, in the course of about 15 sec of 0 3 ml/kg bodyweight of the following cerebrospinal fluid (1 dog) Kontrast U 5, 10 15 20 and 40 % (1 dog each) and saline 5 1 % (1 dog) All the solutions contained 1 mg/ml Xylocaine hydrochloride When the results of this experimental series had been studied the experiment was repeated with Kontrast U 15 % and 20 % and with saline 5 1 % (1 dog each)

The technique used for demonstration of the increase in permeability was essentially the same in relevant details as that of BROMAN & OLSSON (1948) eight minutes after terminating the subarachnoid injection in question 50 ml/kg bodyweight trypan blue 0 5 % were injected i v in the course of 15 minutes The tendency to a fall in blood pressure was counteracted by a continuous slow infusion of noradrenaline solution (20 μg/ml) the dose being 1 4 to 4 μg/kg bodyweight per minute during 12 to 15 minutes When the injection of trypan blue was finished the dogs were heparinized with about 20 mg/kg bodyweight heparin i v After a further 1 to 2 minutes they were killed by i v injection of 6 cg/kg bodyweight pentobarbital sodium (Mebumalnatrium©) 6 %

The chest of the dog was opened and a T tube with an inner diameter of about 5 mm was introduced through an incision in the aorta and fixed with ligatures around the cranial and caudal part of the aorta respectively A cannula of about the same bore was introduced into the right ventricle The cannula was joined by a rubber tube to a container for collecting the outflowing perfusion fluid The T tube was connected to an injection apparatus in which the solution for injection was kept under a pressure of about 150 mm Hg The vascular system was first perfused with physiologic saline until the colour

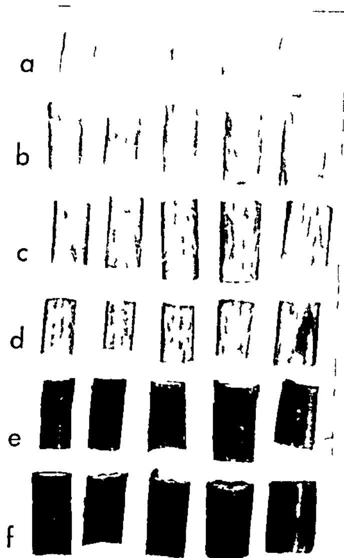


Fig 13 Spinal cord (Th12 L3) of six dogs after i v injection of trypan blue Pretreatment by lumbar subarachnoid injection of cerebrospinal fluid (a) Kontrast U 5 % (b) 10 % (c) 15 % (d) 20 % (e) and 40 % (f) Abrupt increase in the intensity of the blue staining on raising the concentration of the contrast medium from 15 to 20 %

of the fluid from the right ventricle had decreased to a pale pink, and then with 100 ml/kg bodyweight formalin 10 % dissolved in physiologic saline The dog was kept in the refrigerator for 24 hours, after which the spinal cord was exposed and inspected

Results With a rising concentration of contrast medium from 0 to 15 % a successively increasing blue staining of the white matter of the spinal cord was observed (Fig 13) Between 15 and 20 % there was an abrupt increase in colour intensity, with further intensification at 40 % concentration of the medium Repeated experiments with 15 and 20 % concentration of the medium gave staining differences of the same order of magnitude as those in the first experimental series In the dogs given an injection of 5 1 % saline, the intensity of blue staining was inappreciably lower than that observed with contrast medium 20 %

Discussion

Experimental series I formed an attempt to elucidate the influence on the occurrence of spinal cord damage, due to contrast medium, of some conditions which may possibly apply in the clinical use of the preparation In view of the primary observations made in the introduction to this paper, these studies were focused chiefly on the importance of variations in the rate of injection and in the arterial blood pressure The results may be briefly summarized as follows

A moderate fall in blood pressure, i e to about 85 mm Hg after injection of contrast medium did not give rise to any serious functional disturbances or histopathologic changes A marked fall in blood pressure after injection (to about 60 mm Hg) with otherwise identical experimental conditions was on the contrary found to result in severe spinal cord damage in most animals Variations in the rate of injection within the limits stated did not, on the other hand have any apparent effect on the incidence or nature of the damage The most obvious spinal functional disturbances were in the nature of paresis or paralysis of one or both hind legs The morphologic changes in the spinal cord consisted of focal oedema localized to the white matter in the lumbar region and in certain cases, in the thoracic region as well Some of the oedematous foci had a central area of necrosis Both the functional disturbances and the morphologic changes showed a predilection for the side that was in the lower position during injection

These observations seem to warrant the following comments The contribution of the fall in blood pressure to the occurrence of spinal cord damage may be attributable to delayed absorption of contrast medium or to anoxic injuries, which are added to the actual damage caused by the medium The experiments made do not permit any evaluation of the role played by these factors It seems reasonable to infer that the predominant localization of the damage to the right side is due to the fact that the contrast medium in view of its higher specific gravity follows the part of the subarachnoid space lying lowest

The following practical considerations naturally follow The arterial blood pressure should always be checked and if necessary corrected in the diagnostic use of subarachnoid injection of Kontrast U in doses sufficient to reach the spinal cord Turning the animal immediately after ending the examination may be presumed to have a prophylactic effect against damage by the contrast medium since it is then probably diluted more rapidly by the spinal fluid If this procedure is used it further accentuates however, the need for checking the blood pressure This is because positional changes in connexion with injection of contrast medium combined with Xylocaine may produce a severe fall in blood pressure (FUNKQUIST & OBEL 1960)

It is true that injection of contrast medium produced no obvious functional disturbances of the spinal cord in dogs whose blood pressure had been kept close to the normal level Despite this, the presence of morphologic changes in the spinal cord in some of these animals implies that the preparation should not be used for diagnostic purposes under the conditions in question In studies now in progress — of which the results will be published separately — the preparation has been used for thoracolumbar myelography in spontaneous compression of the spinal cord (chiefly prolapsed disc) in the dog The conditions have been modified as follows Elevation of the forequarters has been decreased to about 10 cerebrospinal fluid has not been withdrawn in any appreciable amount before injection of contrast medium the dose has been

reduced to 0 3 ml/kg bodyweight contrast medium 20 % with the addition of 1 mg/ml Xylocaine hydrochloride, turning the dog 90° (from the lateral position onto the abdomen) has been done 1 to 2 minutes after ending the injection Judging by the observations hitherto made, this form of myelography is well tolerated, also as far as structure of the spinal cord is concerned

Experimental series II, which was intended to elucidate the pathogenetic mechanism of the spinal cord damage, was focused *mainly on the problems* (1) whether the disturbances observed in the exchange of fluid within the spinal cord are of primary, decisive importance for the development of the spinal cord lesions or the direct effect of the contrast medium on the non vascular elements of the spinal cord is the more important factor, and (2) whether the injurious effects of the contrast medium are dependent chiefly on osmotic factors, or possibly to a more specific toxic effect

1 The exchange of fluid between the capillaries and the extracellular spaces in the central nervous system is highly sensitive to changes in the osmotic pressure of the blood Intravenous injection of hypotonic saline leads at once to an increased outflow of fluid to the extracellular spaces (WEED 1923), manifested as an increase in volume and raised production of spinal fluid

If the injurious action of the contrast medium were to be dependent mainly on its effect on non vascular elements in the spinal cord, i v injection of hypotonic saline immediately before injection of contrast medium could be expected to result in a more rapid dilution of the medium diffusing into the cord and thus to diminish its injurious effect If, on the other hand, the contrast medium *acted chiefly by promoting the outflow of fluid to the central nervous system*, i v injection of hypotonic saline in connexion with injection of contrast medium could be expected to accentuate the injurious effects

The results of our experiments argue in favour of the latter alternative This is because in dogs pretreated by i v injection of hypotonic saline severe spinal *cord damage appeared after an injection of contrast medium* which under otherwise identical conditions produced no serious damage in dogs that had not been pretreated in this way It seems probable consequently that a disturbance in the exchange of fluid within the spinal cord does in fact play a primary and dominant role in the pathogenesis of damage caused by contrast medium

2 The question whether the contrast medium exerts its injurious effect mainly by osmosis, or by more specific toxic properties, was studied by a comparison between the *effect of contrast medium and that of a saline solution* isotonic with the medium The comparison applied to neurologic symptoms and signs, morphologic changes in the spinal cord and disturbances in the blood spinal cord barrier With respect to functional and morphologic signs of spinal cord lesions, injection of saline was found to produce damage of the same type *and degree of severity* as injection of contrast medium which had the same osmotic pressure and was injected under the same conditions As far as the

effect on the blood spinal cord barrier was concerned the increase in capillary permeability to trypan blue was only inappreciably lower after injection of saline 5 1 % than after injection of Kontrast U 20 %

To sum up the following statements may be made The comparative studies on the effect on subarachnoid injection of saline solution and of contrast medium respectively indicate that the injurious effects of the medium are dependent for the greater part on osmotic factors It is therefore unnecessary to postulate any specific toxic properties of the medium to explain the spinal cord lesions observed The effect of the subarachnoid injection of water soluble contrast medium seems to differ in this way from that of intra arterial injection (cere bral and renal arteriography) since the detrimental effects of contrast medium injected by this route are far more severe than those of saline solution isotonic with it (BROMAN & OLSSON 1949 HELANDER 1958)

Our study of the changes in the blood spinal cord barrier after subarachnoid injection of contrast medium showed a conspicuous abrupt increase in capillary permeability when the concentration of the medium was raised from 15 to 20 % Obviously, this study does not permit any conclusions regarding the importance of the increased capillary permeability for development of the spinal cord lesions However even if the increased permeability were to be a more sub ordinate phenomenon it is difficult to disregard the possibility that it may, in fact be a measure of the injurious effect to which the spinal cord is exposed by the injection of contrast medium If this argument were to be correct, an endeav our should be made to keep the concentration of the medium in the sub arachnoid space at around 15 % or below it On injection of contrast medium 20 % without preceding spinal tap or after withdrawal of only a moderate amount this concentration should be exceeded only for very brief periods If on the other hand the greater part of the spinal fluid is withdrawn before in jection — as has been suggested in cervical myelography (FUNKQUIST 1961) — it seems advisable either to reduce the concentration of the medium to a maxi mum of 15 % or if a higher concentration is used to reinject the spinal fluid as soon as possible

The histopathologic changes in the spinal cord in our experiments are in good agreement with those observed by LUNDY et coll (1933) in the subarach noid injection of highly concentrated procaine in the dog These authors who did not record the blood pressure in their experiments obtained a highly variable effect on the spinal cord even under apparently identical conditions, when discussing the cause of the great diversity in the results they stated that the variations in blood pressure could be ruled out as a factor of importance This was because no correlation existed between the presence of spinal cord lesions and the occurrence of respiratory paralysis and in their opinion the effect of procaine on the respiration and blood pressure should run parallel It does not however seem correct to assume a parallelism between the respira tion depressing effect of procaine and its effect on the blood pressure Conse

reduced to 0 3 ml/kg bodyweight contrast medium 20 % with the addition of 1 mg/ml Xylocaine hydrochloride, *turning the dog 90°* (from the lateral position onto the abdomen) has been done 1 to 2 minutes after ending the injection Judging by the observations hitherto made, this form of myelography is well tolerated, also as far as structure of the spinal cord is concerned

Experimental series II, which was intended to elucidate the pathogenetic mechanism of the spinal cord damage, was focused mainly on the problems (1) whether the disturbances observed in the exchange of fluid within the spinal cord are of primary, decisive importance for the development of the spinal cord lesions or the direct effect of the contrast medium on the non vascular elements of the spinal cord is the more important factor, and (2) whether the injurious effects of the contrast medium are dependent chiefly on osmotic factors, or possibly to a more specific toxic effect

1 The exchange of fluid between the capillaries and the extracellular spaces in the central nervous system is highly sensitive to changes in the osmotic pressure of the blood Intravenous injection of hypotonic saline leads at once to an increased outflow of fluid to the extracellular spaces (WEED 1923), manifested as an increase in volume and raised production of spinal fluid

If the injurious action of the contrast medium were to be dependent mainly on its effect on non vascular elements in the spinal cord, i v injection of hypotonic saline immediately before injection of contrast medium could be expected to result in a more rapid dilution of the medium diffusing into the cord, and thus to diminish its injurious effect If, on the other hand, the contrast medium acted chiefly by promoting the outflow of fluid to the central nervous system, i v injection of hypotonic saline in connexion with injection of contrast medium could be expected to accentuate the injurious effects

The results of our experiments argue in favour of the latter alternative This is because in dogs pretreated by i v injection of hypotonic saline severe spinal cord damage appeared after an injection of contrast medium which under otherwise identical conditions produced no serious damage in dogs that had not been pretreated in this way It seems probable consequently that a disturbance in the exchange of fluid within the spinal cord does in fact play a primary and dominant role in the pathogenesis of damage caused by contrast medium

2 The question whether the contrast medium exerts its injurious effect mainly by osmosis, or by more specific toxic properties, was studied by a comparison between the effect of contrast medium and that of a saline solution isotonic with the medium The comparison *applied to neurologic symptoms and signs*, morphologic changes in the spinal cord and disturbances in the blood spinal cord barrier With respect to *functional and morphologic signs of spinal cord lesions*, injection of saline was found to produce damage of the same type and degree of severity as *injection of contrast medium* which had the same osmotic pressure and was injected under the same conditions As far as the

effect on the blood spinal cord barrier was concerned, the increase in capillary permeability to trypan blue was only inappreciably lower after injection of saline 5 1 % than after injection of Kontrast U 20 %

To sum up the following statements may be made The comparative studies on the effect on subarachnoid injection of saline solution and of contrast medium respectively indicate that the injurious effects of the medium are dependent for the greater part on osmotic factors It is therefore unnecessary to postulate any specific toxic properties of the medium to explain the spinal cord lesions observed The effect of the subarachnoid injection of water soluble contrast medium seems to differ in this way from that of intra arterial injection (cere bral and renal arteriography) since the detrimental effects of contrast medium injected by this route are far more severe than those of saline solution isotonic with it (BROMAN & OLSSON 1949 HELANDER 1958)

Our study of the changes in the blood spinal cord barrier after subarachnoid injection of contrast medium showed a conspicuous abrupt increase in capillary permeability when the concentration of the medium was raised from 15 to 20 % Obviously this study does not permit any conclusions regarding the importance of the increased capillary permeability for development of the spinal cord lesions However even if the increased permeability were to be a more sub ordinate phenomenon it is difficult to disregard the possibility that it may in fact be a measure of the injurious effect to which the spinal cord is exposed by the injection of contrast medium If this argument were to be correct an endeav our should be made to keep the concentration of the medium in the sub arachnoid space at around 15 % or below it On injection of contrast medium 20 % without preceding spinal tap or after withdrawal of only a moderate amount this concentration should be exceeded only for very brief periods If, on the other hand the greater part of the spinal fluid is withdrawn before in jection — as has been suggested in cervical myelography (FUNKQUIST 1961) — it seems advisable either to reduce the concentration of the medium to a maxi mum of 15 % or if a higher concentration is used, to reinject the spinal fluid as soon as possible

The histopathologic changes in the spinal cord in our experiments are in good agreement with those observed by LUNDY et coll (1933) in the subarach noid injection of highly concentrated procaine in the dog These authors, who did not record the blood pressure in their experiments obtained a highly variable effect on the spinal cord even under apparently identical conditions when discussing the cause of the great diversity in the results they stated that the variations in blood pressure could be ruled out as a factor of importance This was because no correlation existed between the presence of spinal cord lesions and the occurrence of respiratory paralysis and in their opinion the effect of procaine on the respiration and blood pressure should run parallel It does not however, seem correct to assume a parallelism between the respira tion depressing effect of procaine and its effect on the blood pressure Conse

quently, it seems likely, in view of the results of our experiments, that the combination of low arterial blood pressure and the presence of a hypertonic solution in the subarachnoid space may, in fact, have played a pathogenetic role in the damage to the spinal cord produced by procaine in the experiments of LUNDY et coll Moreover, we consider that it is advisable, in an analysis of the neurologic complications of spinal anaesthesia, to pay more regard to the blood pressure conditions during anaesthesia than seems hitherto to have been the case Another consideration is the possibility of the parenteral administration, before or during anaesthesia, of solutions with a low electrolyte content

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SUMMARY

The effect on the spinal cord of filling the greater part of the spinal subarachnoid space with Kontrast UO 20 % has been studied under experimental conditions in dogs It was found that the incidence and severity of the spinal cord lesions could be increased by lowering the blood pressure after injection and by the previous i v injection of hypotonic saline Subarachnoid injection of saline solution isotonic with the contrast medium was found to produce spinal cord lesions of the same type as did the contrast medium

ZUSAMMENFASSUNG

Die Wirkung einer Fullung des grossten Teiles des spinalen Subarachnoidalraumes mit Kontrast UO 20 % auf das Ruckenmark ist unter experimentellen Bedingungen bei Hunden untersucht worden Man fand dass die Haufigkeit und die Schwere der Ruckenmarkschadigung durch Herabsetzung des Blutdruckes nach der Injektion und durch vorherige intravenose Injektion hypotoner Salzlosung gesteigert werden konnte Es ergab sich dass die subarachnoidale Injektion einer mit dem Kontrastmittel isotonen Salzlosung Ruckenmarkschadigungen des gleichen Typus wie das Kontrastmittel selbst hervorruft

RÉSUMÉ

Les auteurs ont étudié dans des conditions expérimentales sur des chiens l effet sur la moelle épinière du remplissage de la majeure partie de l espace sous arachnoidien rachidien avec du Kontrast UO à 20 % Ils ont constaté qu on peut augmenter la fréquence et la gravité des lésions médullaires en abaissant la tension artérielle apres l injection et en injectant préalablement par voie intraveineuse une solution saline hypotonique Ils ont constaté que l injection sous arachnoidienne d une solution saline isotonique au moyen de contraste produit des lésions médullaires de même type que celles que cause le moyen de contraste

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FROM THE EDWARD MALLINCKRODT INSTITUTE OF RADIOLOGY AND THE DEPARTMENT OF PEDIATRICS, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, SAINT LOUIS 10, MISSOURI, U S A

SUPRAVALVULAR STENOSES OF THE PULMONARY ARTERIES

Report of eleven cases

by

HAKAN ARVIDSSON, ERIK CARLSSON, ALEXIS HARTMANN, JR, ARGYRIOS TSIFUTIS and CHARLES CRAWFORD

The widespread use of cardiac catheterization and especially selective angiocardiography has made it possible to diagnose unusual cardiac malformations ante mortem Supravalvular pulmonary artery stenoses are good examples of this, and single case reports and small collections of cases have been reported so that at present there are 41 instances of these malformations described in the literature (1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 16, 17, 18, 21, 22, 25)

Some of the cases reported had isolated supravalvular stenoses, others had associated heart malformations, such as pulmonary valvular stenoses, patent ductus arteriosus, interventricular and interatrial septal defects There is only one report upon the pathologic findings (ORELL et coll)

A clearer conception of these malformations may be gained by reviewing the classification proposed by SMITH, who divided the supravalvular stenoses to three groups

in *Type I* Single or multiple stenoses of the pulmonary arteries These are usually situated in the lobar branches in the hilar region but may be present in relatively small extrahilar branches Poststenotic dilatations are usually present (1, 4, 6, 7, 8, 18, 21, 22, 25)

Type II Stenosis of the bifurcation of the pulmonary trunk (16, 17)

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Type III Membranous stenosis immediately distal to the pulmonary valve (9 11 20)

To this classification a fourth group may be added

Type IV Stenosis or generally diminished cross sectional area of the pulmonary arteries usually the right (12)

Combinations of the four types have also been observed

The purpose of this study is to report 11 patients with supravalvular stenoses diagnosed by selective angiocardiography This is the largest number of patients studied in one series, and provides an unusual opportunity to re emphasize the clinical recognition, diagnostic approach and prognosis in patients born with these malformations

Material and Methods The material consists of eleven patients ranging in age from 10 months to 18 years All patients were completely evaluated prior to catheterization and angiocardiography The data will be found in the following Case reports The catheterizations were performed with USCI heart catheter after a venous cut down and oxygen saturation was measured with a Waters cuvette oximeter In 2 instances it was possible to obtain oxygen samples from the aorta after the catheter had passed through a patent ductus arteriosus Pressures were recorded with a Statham string gauge manometer In 10 of the cases the pressure gradients over the stenotic areas were not recorded This was due to the fact that the correct diagnosis was often not suspected until the angiocardiograms were seen

Angiocardiography was performed immediately after the catheterization study The tip of the catheter was placed either in the main pulmonary artery or in the right ventricle and Hypaque® 75 per cent a dose of 1 2 to 1 5 ml/kg body weight was injected with a Gidlund pressure syringe The film changer was of the Schonander type biplane 24 × 30 cm with a maximum exposure frequency of 6 per second Two 4 valve Picker generators were used operated with Dynapulse allowing an exposure time of 5 milliseconds The program selector of the film changer was arranged so that films were obtained during the filling of the right as well as the left heart and the aorta Simultaneous recordings of the ECG and exposures were made so as to secure the cardiac phase of each pair of films On the films the smallest cross-sectional areas of the main pulmonary artery and the right and left pulmonary arteries were measured The arteries were measured on films exposed in ventricular systole and the areas were corrected for the geometrical distortion As a comparison the cross sectional area of the ascending aorta was determined according to the same principles

Case reports

Case 1 Girl aged five and a half years coloured Father AET 31 and mother AET 26 both without heart disease (Two siblings (Cases 2 and 3) diagnosed as multiple peripheral pulmonary artery stenoses Male sibling died when one month old of undiagnosed heart disease male sibling aged 2 years and female sibling aged 7 months have no evidence of heart disease) A heart murmur was detected when patient was six months old She is asymptomatic except that she easily tires and has respiratory infections with increasing frequency

Physical examination Height 108 cm weight 18 4 kg auxodrome 42 Wetzel grid Grade 2/4 systolic murmur present at bases R > L transmitted to axillae and back O_2 saturation 93 hemoglobin 12 6 g ECG right ventricular enlargement

Roentgenograms of chest Signs of right ventricular enlargement The central pulmonary arteries appeared wide the peripheral arteries normal

Cardiac catheterization Oxygen saturation determination no left to-right shunt Pressures right ventricle 49/0 and main pulmonary artery 49/8

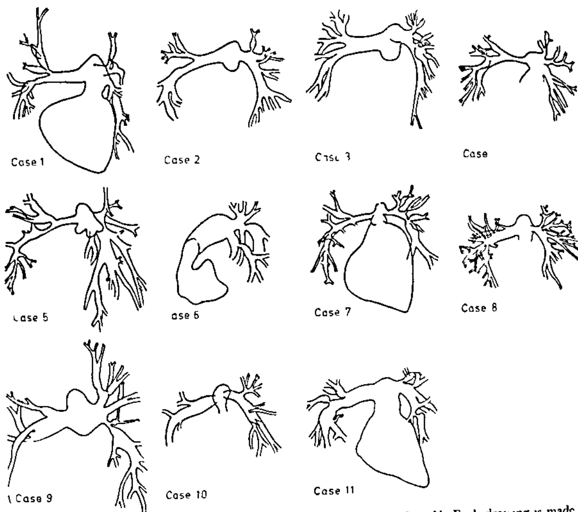


Fig 1 Schematic drawings of angiocardiographic patterns in Cases 1 to 11 Each drawing is made from several films some details are better seen in an early phase others in a late phase of the examination All drawings are from anteroposterior films except in Case 6 which is a drawing from a lateral projection

Angiocardiography with injection into right ventricle (see Figs 1 and 2) Right ventricular enlargement pulmonary valves normal Main pulmonary artery normal in appearance but right pulmonary artery hypoplastic The left pulmonary artery was not accessible for measurements as masked by the main pulmonary artery Multiple peripheral stenoses with marked poststenotic dilatations were present on both sides

Cross sectional areas Main pulmonary artery 1 65 cm² right pulmonary artery 0 33 cm² left pulmonary artery not accessible aorta 0 8 cm²

Diagnosis Multiple peripheral stenoses and hypoplasia of right pulmonary artery

Case 2 Boy aged 20 months coloured For family history see Case 1 Entered for evaluation because of heart murmur first heard at age of 12 months Increasing number of upper respiratory infections

Physical examination Height 70 cm weight 11 9 kg auxodrome 50 % Wetzel grid Grade 2/4 systolic murmur loudest at right base and left sternal border transmitted well to axillae back and neck O_2 saturation 90 % hemoglobin 10 3 g % ECG right ventricular enlargement

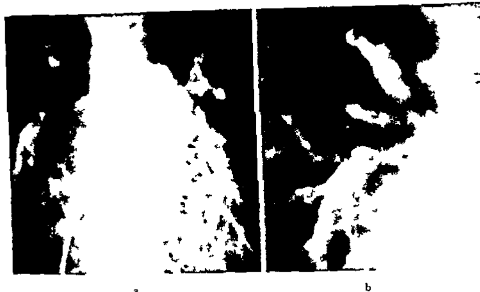


Fig 2 Case 1 Angiocardiography ant ropo teri r projection Inj ction into right ventricle a) Narrow right and left pulm nary arte es b) Detail f r ght pulmonary artery St noses at the b f cations with post tenotic d latat ons The stenoses are not well seen in the lower and m ddle lobe a ter es due to superimpositi n but th po tstenot c d latations are isible

R ut ne roentgenograms of chest Moderate left atrial enlargement and possibly some right atrial enlargement Main and peripheral pulmonary arteries of normal appearance

Cardiac catheter ation Oxygen saturation determination no left to-right shunt Pressures right ventricle 39/0 main pulmonary artery 39 8

An ioca diography with injection into main pulmonary artery (see Fig 1) Moderate nar rowing of pulmonary artery mainly in both upper lobes During the filling of the left side of the heart there was marked left atrial and ventricular enlargement and the aortic valves were deformed Moderate aortic valvular stenosis could not be exluded

Cross sectional areas Main pulmonary artery 0 55 cm² right pulmonary artery 0 40 cm² left pulmonary artery 0 30 cm and aorta 0 55 cm²

Diagnosis Multiple peripheral pulmonary stenoses and (?) aortic valvular stenosis

Case 3 G rl aged two and a half years coloured Family history see Case 1 Entered for evaluation because of increasing tiredness and a heart murmur first heard in the neonatal pe riod

Physical exami ation Height 86 cm weight 13 5 kg auxodrome 67 ° Wetzel grid Grade 3/4 systolic murmur at left sternal border loudest at 3rd 4th and 5th interspaces transmitted to left axilla and back O_2 saturation 93 hemoglobin 11 0 g ₀ ECG normal

Routine roentgenog ams of chest Heart normal in size and shape pulmonary vessels normal

C diac cathete i ation Oxygen saturation determination no left to-right shunt Pressures right ventricle 36 0 main pulmonary artery 34/7

A g oca d og aphy with injection into main pulmonary artery (see Fig 1) Main pulmonary artery and pulmonary valves normal Stenoses in practically all branches of the pulmonary arteries Normal left atrium ventricle and aorta

Cr ss secti n l a eas Main pulmonary artery 1 35 cm right pulmonary artery 0 9 cm² left pulmonary artery 0 7 cm² and aorta 1 0 cm²

Diagno is Mult ple peripheral pulmonary stenoses

Case 4 Girl aged 10 months coloured Born prematurely, birth weight 1 970 g Mother had rubella during the first trimester Heart murmur discovered at age of 4 months

Physical examination Small infant, height 67 5 cm weight 5 0 kg premature auxodrome on Wetzel grid Grade 3/4 continuous murmur at left base with systolic thrill O_2 saturation (earpiece) 96 % hemoglobin 11 0 g % ECG left ventricular enlargement *patent ductus* arteriosus divided and sutured (age 10 months) Since operation asymptomatic but had a grade 1—2/4 systolic murmur at left sternal border transmitted to axillae and back

Routine roentgenograms of chest Before ligation of patent ductus arteriosus wide pulmonary vessels enlarged left atrium wide ascending aorta and suggestion of left ventricular enlargement No evidence of pulmonary valvular stenosis After operation the pulmonary arterial vessels were considerably narrower than previously Aorta was narrower than before ligation but there was still some enlargement of the left atrium No signs of right ventricular enlargement

Cardiac catheterization Oxygen saturation determination no left to right shunt Pressures right ventricle 70/0 main pulmonary artery 57/27 There was thus a slight systolic gradient between the right ventricle and pulmonary artery this was undoubtedly produced by the L—R shunt through the patent ductus arteriosus

Angiocardiography injection into right ventricle (see Fig 1) Fused pulmonary valves forming a dome during ventricular systole Diastolic dilution effect in the main pulmonary artery consistent with patent ductus arteriosus Marked narrowing of right pulmonary artery and multiple peripheral stenoses with poststenotic dilatations

Cross sectional areas Main pulmonary artery 1 0 cm^2 right pulmonary artery 0 08 cm^2 left pulmonary artery 0 12 cm^2 and aorta 0 9 cm^2

Diagnosis Multiple peripheral pulmonary stenoses Hypoplasia of right pulmonary artery pulmonary valvular stenosis and patent ductus arteriosus

Case 5 Girl aged 9 years, white Mother had rubella during the first six weeks of gestation Congenital cataracts were noted at birth and a heart murmur at the age of six months At the age of four patient was admitted because of cardiac failure refractory to digitalis oxygen and diuretics A patent ductus arteriosus was diagnosed clinically on the basis of a continuous murmur at base of heart A 7 mm diameter patent ductus was ligated as a desperation measure in spite of cardiac failure She improved markedly after operation and became asymptomatic except for intolerance to mild exercise a systolic murmur and residual cardiac enlargement She was readmitted at the age of nine years for evaluation

Physical examination Small child height 123 cm weight 22 6 kg auxodrome 90 % Wetzel grid Bilateral postoperative cataracts A grade 2/4 systolic murmur over the entire precordium loudest at right base O_2 saturation 97 % hemoglobin 12 9 g % ECG signs of biventricular enlargement and myocardial disease

Routine roentgenograms of chest Before operation general cardiac enlargement with left ventricular and right ventricular enlargement wide pulmonary vessels and attenuation of the vessels in the middle zones of the lungs Following operation still some signs of right ventricular enlargement Central pulmonary vessels wide but peripheral vessels narrow Rounded mass close to the descending aorta (?) postoperative aneurysm

Cardiac catheterization (postoperative) Oxygen saturation determination no left to right shunt Pressures right ventricle 61/0 main pulmonary artery 53/12

Angiocardiography with pulmonary artery injection (see Fig 1) Mild pulmonary valvular stenosis with thickening of valves and dome formation during ventricular systole Multiple peripheral stenoses of pulmonary arteries particularly on right side Postoperative aneurysm of descending aorta filled simultaneously with the aorta

Cross sectional areas Main pulmonary artery 1 3 cm^2 right pulmonary artery 0 23 cm^2 left pulmonary artery 0 47 cm^2 and aorta 2 5 cm^2

Diagnosis Multiple peripheral pulmonary stenoses Postoperative patent ductus arteriosus with aneurysm of aorta Mild pulmonary valvular stenosis



Fig 3 Case 7 Angiocardiography anteroposterior projection Injection into right ventricle Typical appearance of the stenoses and poststenotic dilatations which are best seen in the arteries of the upper lobes

Case 6 Girl aged three and a half years white Mother had rubella during third week of pregnancy Born prematurely birth weight 1 391 g Heart murmur and bilateral cataracts detected during neonatal period She was entered for evaluation because of heart murmur frequent upper respiratory infections and retarded growth

Physical examination Small child height 83 cm weight 9 6 kg auxodrome very premature according to Wetzel grid Grossly enlarged heart with bulging left hemithorax Grade 3/4 harsh systolic and diastolic murmur at left base Second systolic murmur with systolic thrill at left lower sternal border O_2 saturation (earpiece) 97 % hemoglobin 12 5 g % ECG right ventricular enlargement and incomplete right bundle branch block

Routine roentgenograms of chest General enlargement of heart particularly of left atrium and left ventricle Wide pulmonary vessels compatible with left to-right shunt

Cardiac catheterization Oxygen saturation determination left to-right shunts at atrial and ventricular levels Pressures right ventricle 83/0 the pulmonary artery could not be entered

Angiocardiography with right ventricular contrast medium injection (see Fig 1) Thickened pulmonary valves forming a dome during ventricular systole Some local stenoses evident in lateral view in lungs Contrast medium passed from the right to the left ventricle during the injection Dilution effect in main pulmonary artery consistent with patent ductus arteriosus

Cross sectional areas Main pulmonary artery 2 2 cm² right pulmonary artery not accessible left pulmonary artery 0 3 cm² and aorta 1 2 cm²

Course The patient died with complete heart block immediately after surgical repair of interventricular septal defect and patent ductus arteriosus Autopsy verified the diagnostic findings

Diagnosis Multiple peripheral pulmonary stenoses ventricular septal defect patent ductus arteriosus and pulmonary valvular stenosis

Case 7 Boy aged two and a half years White Heart murmur and syndactylism of left hand present at birth At the age of 3 weeks pylorotomy was successfully performed for pyloric stenosis He was entered for evaluation because of the murmur and an episode of syncope

Physical examination Height 91 cm weight 14 kg auxodrome 50 % Wetzel grid Syndactylism of left hand involving three digits Grade 3—4/4 systolic murmur over the entire precordium loudest at second left interspace transmitted to axillae and back A systolic thrill was palpable at 3rd to 4th left interspaces The pulmonary second sound was diminished O_2 saturation was 97 % hemoglobin 12 3 g % ECG right ventricular enlargement

Routine roentgenograms of chest Some right ventricular enlargement Wide and irregular central pulmonary vessels and narrow and irregular peripheral vessels Narrow aorta

Cardiac catheterization Oxygen saturation determination no left to right shunt Pressure right ventricle 78/0

Angiocardiography Right ventricle injected (see Figs 1 and 3) Pulmonary valves slightly deformed possibly with some stenosis Both right and left pulmonary arteries narrow with local stenoses and poststenotic dilatations of practically all branches During filling of aorta a local reduction in size of ascending aorta above the aortic valves was noted

Cross sectional areas Main pulmonary artery 0 56 cm², right pulmonary artery 0 14 cm² left pulmonary artery 0 12 cm², and aorta 0 8 cm

Course The patient died suddenly at home two months after the investigation No autopsy performed

Diagnosis Multiple peripheral pulmonary stenoses Pulmonary valvular stenosis and supravalvular aortic stenosis

Case 8 Boy aged 5 years white Entered for evaluation because of heart murmur detected on routine physical examination at school and increasing frequency of upper respiratory infections

Physical examination Well developed acyanotic boy height 100 cm weight 18 2 kg auxodrome 40 % Wetzel grid Grade 2/4 systolic murmur at bases R > L transmitted to axillae and back R > L hemoglobin 11 9 g % ECG possibly right ventricular enlargement

Routine roentgenograms of chest Slight cardiac enlargement mainly of left ventricle and left atrium Irregular peripheral pulmonary vessels

Cardiac catheterization Oxygen saturation determination no left to right shunt Pressures right ventricle 54/0 main pulmonary artery 54/7

Angiocardiography Pulmonary artery injected (see Fig 1) Narrow left pulmonary artery Peripheral pulmonary stenoses mainly of smaller branches particularly on right side Left ventricle considerably enlarged and during its filling possibly some of the medium lies in the right ventricle The changes in the diameter of the ascending aorta from systole to diastole are much greater than usual and suggest aortic insufficiency

Cross sectional areas Main pulmonary artery 1 3 cm² right pulmonary artery 0 8 cm² left pulmonary artery 0 2 cm² and aorta 1 5 cm²

Diagnosis Multiple peripheral stenoses (?) aortic insufficiency and (?) ventricular septal defect

Case 9 Male aged 18 years white Entered for evaluation because of heart murmur first detected at age of 20 months Asymptomatic

Physical examination Grade 3/4 systolic murmur and thrill at left base Hemoglobin 14 7 g % ECG right ventricular enlargement

Routine roentgenograms of chest Heart volume not increased but main pulmonary artery and central and peripheral pulmonary vessels all wide suggesting a left to right shunt

Cardiac catheterization Oxygen saturation determination no left to right shunt Pressures right ventricle 80—90/5 left pulmonary artery 30—33/10

Angiocardiography Pulmonary artery injected (see Figs 1 and 4) Considerable local stenosis



F 4 Case 9 Angiocardiography lateral view Right ventricle and atrium contrast filled. The pulmonary valves are closed (diastole) and are normal in appearance There is a diaphragmatic supravalvular stenosis in the main pulmonary artery (arrow)



Fig 5 Case 11 Angiocardiography anteroposterior view Right ventricle injected Both the right and left pulmonary arteries are relatively narrow Stenoses and poststenotic dilatations particularly in right upper lobe arteries

of main pulmonary artery due to diaphragmatic formation above the valves Multiple peripheral pulmonary stenoses with poststenotic dilatations particularly on left side

Cross sectional areas Main pulmonary artery (at area of stenosis) 0 8 cm² right pulmonary artery 1 7 cm² left pulmonary artery 1 3 cm and aorta 4 5 cm²

Diagnosis Multiple peripheral pulmonary stenoses and stenosis of main pulmonary artery

Case 10 Boy aged 5 years coloured Mother s pregnancy uneventful birth normal Deafness and heart murmur apparent at age of 21 months Entered for diagnostic studies because of decreased exercise tolerance and slight cardiac enlargement

Physical examination Acyanotic Height 114 cm weight 16 8 kg auxodrome 50 a Wetzel grid Grade 2/4 systolic murmur at bases R > L transmitted to axillae and back Systolic thrill at right base Hemoglobin 11 5 g ECG within normal limits

Routine roentgenograms of chest Slight cardiac enlargement with predominance of right ventricle Wide pulmonary vessels suggesting left to-right shunt

Cardiac catheterization Oxygen saturation determination no left to-right shunt Pressures right ventricle 45/0 main pulmonary artery 41/10 and left pulmonary artery 26/0

Angiocardiography Pulmonary artery injected (see Fig 1) Stenosis at bifurcation of main pulmonary artery with a high degree of stenosis of left pulmonary artery Left side of heart normal except for moderate deformity and thickening of the aortic valves but no signs of stenosis (No poststenotic dilatation of ascending aorta)

Cross sectional areas Main pulmonary artery 1 9 cm² right pulmonary artery 0 5 cm² left pulmonary artery 0 25 cm² and aorta 2 1 cm

Diagnosis Coarctation of pulmonary artery

Case 11 Boy, aged 15 years coloured Heart murmur present 8 months prior to admission Symptoms palpitations on extreme exertion but participates in athletics

Physical examination Well developed well nourished boy, height 165 cm weight 55 kg Grade 2/4 systolic murmur at bases transmitted to axillae and back Hemoglobin 13 g % ECG possibly slight right ventricular enlargement

Routine roentgenograms of chest Heart normal in size and shape Prominent hilar vessels but not of the L—R shunt type Peripheral pulmonary vessels normal to slightly decreased in size

Cardiac catheterization Oxygen saturation determination inconclusive Pressures right ventricle 70/4 main pulmonary artery 70/8, right pulmonary artery peripherally 20/10 right pulmonary artery centrally 50/10, left pulmonary artery peripherally 20/10

Angiocardiography Right ventricle injected (see Figs 1 and 5) Pulmonary valves normal considerable changes in diameter of main pulmonary artery Multiple peripheral stenoses mainly of arteries of upper lobes Normal left atrium left ventricle and aorta

Cross sectional areas Main pulmonary artery 4 5 cm² right pulmonary artery 0 7 cm² left pulmonary artery 0 2 cm² and aorta 3 5 cm²

Diagnosis Multiple peripheral pulmonary stenoses

Results

A Clinical findings It is difficult to establish the diagnosis of multiple peripheral pulmonary stenoses by physical examination, but the murmur which is systolic and often in an unusual location and distribution, may make one suspect the diagnosis In four patients (Cases 1, 2, 5 and 10), the murmur was heard best at the right base, and was transmitted well to both axillae and the back This raised the question of an aortic valve lesion prior to angiocardiography, even though the aortic second sound was normal In Case 7, supravalvular aortic stenosis did, in fact, exist in addition to the multiple peripheral pulmonary stenoses, and the aortic lesion probably was responsible for the syncopal episode and sudden death of this child In Case 2, there was a deformity of the aortic valves but no evidence of aortic stenosis

A continuous murmur occurring with isolated peripheral pulmonary stenoses has been described by several authors (*1, 5, 8, 9, 18, 21*) and 2 patients reported (5, 8) were operated on for patent ductus arteriosus before the correct diagnosis was established None of the patients in this series with isolated peripheral stenoses had a continuous murmur However, Cases 4 and 5 had a continuous murmur before ligation of a concomitant patent ductus arteriosus The murmur compatible with multiple pulmonary peripheral stenoses was heard only after ligation of the ductus arteriosus in these two patients

In the isolated disease the electrocardiogram usually shows right ventricular enlargement, but may be normal if the disease is minimal (Cases 3 and 10) The electrocardiographic findings may be influenced by an associated lesion, e g patient represented in Case 4 who also had a patent ductus arteriosus and left ventricular enlargement It is interesting to note that after ligation of the patent ductus arteriosus the ECG was interpreted as normal

B Conventional chest roentgenograms The findings on the chest roentgenograms in cases of multiple stenoses of the pulmonary artery or coarctation of the pulmonary artery are generally inconclusive The increased pressure in the pulmonary artery and right ventricle are associated with right ventricular hypertrophy and dilatation The central pulmonary vessels may, or may not appear widened The stenoses themselves are impossible to locate on the conventional films even when compared with the angiocardiograms This is partly due to superimposition of the pulmonary veins hiding the stenoses In cases with very marked poststenotic dilatations of the peripheral pulmonary arteries the pulmonary vessels may have the appearance of a left to right shunt (Case 9) There is usually a moderate dilatation of the main pulmonary artery The above description is only valid if no associated lesions exist and if there is a congenital defect the appearance of the conventional chest films will be affected In a case of patent ductus arteriosus and multiple stenoses for instance the signs of overcirculation of the lungs dilatation of the arch and ascending aorta left atrial and left ventricular enlargement will be encountered In cases combined with valvular pulmonary stenosis, the main pulmonary artery and central pulmonary branches will be dilated

C Cardiac catheterization Catheterization of the pulmonary arteries is of value in the diagnosis of multiple peripheral stenoses In some of the cases reported (19 23) the diagnosis was established only by means of a catheter pull out curve from a peripheral to the main pulmonary artery It seems unreliable to base the diagnosis on pressure measurements alone This is particularly true for the peripheral pulmonary stenoses (type I) The catheter may not pass the area of constriction and a diagnosis of idiopathic or primary pulmonary hypertension may be made erroneously If the catheter is partly wedged in a peripheral artery a diagnosis of a non existent peripheral stenosis may be made The central stenoses are less apt to be misdiagnosed by the catheter method Even if the diagnosis of peripheral stenoses is established by catheterization angiocardiography should also be performed for this will confirm the diagnosis and additional narrowings may thus be detected

All patients in this series had elevated systolic pressures in the right ventricle The pressures were higher in cases with combined lesions than in the patients with isolated supravalvular stenoses The pressure gradients over the stenotic areas were recorded in only 3 patients (Cases 9 10 and 11) In the 3 patients that had associated pulmonary valvular stenosis the main pulmonary artery was catheterized in only one patient (Case 4) and the pressure was significantly increased in the main pulmonary artery in spite of the pulmonary valvular stenosis

D Angiocardiography Angiocardiography is the best method for demonstrating peripheral pulmonary stenoses The use of a selective injection of contrast medium in the pulmonary artery or right ventricle is preferable to a

venous angiocardiogram When the venous injection method is used, parts of the pulmonary arteries are often hidden by contrast media in the right heart and systemic veins, but the selective angiocardiogram shows the details of the pulmonary arteries The diagnosis of the pulmonary stenoses of the central types (II, III, and IV) offers little difficulty as it can usually be seen both in the anteroposterior and lateral projections The peripheral stenoses, however, are sometimes difficult to detect even on a good standard angiocardiogram This is due to the fact that the stenoses, which sometimes are of very thin diaphragmatic type, may not be located either in the anteroposterior or lateral planes This means that the pre- and poststenotic segments are superimposed in both projections and thus hiding the stenoses In this type of stenosis the significant sign is the poststenotic dilatation, i e, the pulmonary arteries are wider in the mid parts of the lungs than centrally, as demonstrated by Fig 1, in Cases 4 and 7, where the spindle shaped poststenotic dilatations of the pul monary vessels are, as a matter of fact, in several arteries the only sign of stenosis

The catheterization data gives clues as to concomitant heart lesions A left to right shunt is detected by the oxygen saturation measurements and a valvular pulmonary stenosis is shown by a systolic gradient over the valves Such findings govern the site of the contrast injection If a ventricular septal defect or pul monary valvular stenosis is suspected, the injection should be performed in the right ventricle If the pulmonary stenoses seem to be isolated or combined with a left heart malformation, e g aortic stenosis, the injection is preferably made into the main pulmonary artery so that the lower lobe arteries on the left lung are not obscured by contrast in the right ventricle

Discussion

Etiology ARVIDSSON et coll (1) described two cases in the same family, mother and son, with multiple peripheral stenoses of the pulmonary arteries In 1957, VAN EPPS (21) reported two brothers with pulmonary hypertension who both had stenoses in the peripheral pulmonary arteries The present material in cludes three siblings with multiple stenoses of the pulmonary arteries Thus there seems to be a familial factor in this disease Familial incidence of con genital heart disease has been reported earlier (10, 23)

Two cases have been reported earlier in which the mother had rubella during pregnancy, one by GYLLENSWARD et coll (9) and one by WILLIAMS, LANGE and HECHT (25) In the present material there are three cases in which the mother had rubella during the first trimester Thus, 5 out of the 52 cases reported in the literature have been associated with maternal rubella There are numerous reports on the occurrence of congenital heart disease, especially patent ductus arteriosus, following maternal rubella (2, 15, 19 24)

There is strong evidence that multiple peripheral stenoses are congenital malformations and not acquired defects as a result of a disease such as multiple

recanalized pulmonary emboli and therefore should not be classified as primary pulmonary hypertension as advocated by VAN EPPS

The central pulmonary arteries The cross sectional areas of the central pulmonary vessels and aorta are given in the Case reports The area of the ascending aorta is given as a measure of the size of the patients Normally the ascending aorta has about the same cross sectional area as the main pulmonary artery As can be seen from the figures the cross sectional areas of the central pulmonary arteries were often considerably reduced The right pulmonary artery was considerably narrowed in five patients (Cases 1 4 5 7, 10) and the left narrowed in five patients (Cases 4, 6 7, 8 10) One of the patients (Case 10) had the classical features of coarctation of the pulmonary artery The main pulmonary artery had a considerably reduced cross section area in Case 7 (see Fig 3) due to a diaphragmatic supravalvular stenosis (type III) The comparison between the areas of the aorta and main pulmonary artery is evidently of limited value in cases with pulmonary valvular stenosis because of the associated poststenotic dilatation of the main pulmonary artery Generally, it can be stated that the central pulmonary arteries have a reduced cross sectional area in cases of multiple pulmonary peripheral stenoses In the present material there is an equal frequency of right and left sided central narrowings, but LUAN et coll (12) claims that right sided lesions are more common

Pulmonary hypertension Pulmonary hypertension is present in all cases of multiple peripheral pulmonary stenoses and pulmonary coarctation reported except for cases with concomitant pulmonary valvular stenosis The hypertension in the lesser circulation might be explained by mechanical obstruction of the pulmonary flow as in valvular pulmonary stenosis The degree of pulmonary hypertension seems to be related to the degree of peripheral stenosis in the pulmonary arteries However FALKENBACH et coll (6) in an excellent survey of the malformation presented evidence that the effect of the stenosis is not only a mechanical one but there also must exist another factor producing pulmonary hypertension The above mentioned authors produced partial obstruction of the left pulmonary artery in puppies and found persistently elevated right ventricular pressure up to one year after the ligation This is not the case when a pulmonary artery is totally occluded The authors discuss a Goldblatt effect of the lungs and say that it appears to be related to pulmonary ischemia This is a very interesting observation which however needs further study

Conclusions

Multiple peripheral pulmonary stenoses is a congenital anomaly which may be isolated or combined with any other intra or extracardiac anomaly A satisfactory embryologic explanation of malformation is lacking

The clinical findings are generally *inconclusive* in the isolated cases Usually there is a systolic or continuous murmur best heard at the base and the *murmur is widely transmitted* to the axilla and back The auscultatory findings may simulate aortic valvular stenosis when the murmur is loudest at the right base, *and a continuous* murmur may mimic that of a patent ductus arteriosus This congenital malformation can be diagnosed by cardiac catheterization in combination with selective angiocardiography If only catheterization is performed the multiple peripheral stenoses may mistakenly be diagnosed as *primary* pulmonary hypertension, but selective angiocardiography will establish the correct diagnosis

No treatment is available for the multiple peripheral stenoses but surgical *correction has been performed in cases with central stenoses (20) The prognosis* is unknown, but probably depends upon the severity of the stenoses and the presence of associated lesions Additional defects compound the severity of the clinical condition, as was demonstrated in the two patients who died, one had aortic stenosis and the other a ventricular septal defect and a patent ductus arteriosus Correction of associated lesions may definitely improve the prognosis, as was demonstrated by the patient in Case 5 who was in severe failure until a patent ductus arteriosus was ligated

SUMMARY

Eleven patients with supravalvular pulmonary stenoses are presented all diagnosed by selective angiocardiography Five had no demonstrable heart anomaly Four different types of stenoses were distinguished single or multiple stenoses of the lobar branches of the pulmonary artery stenosis at the bifurcation of the pulmonary trunk membranous stenosis immediately distal to the pulmonary valve stenosis or generally diminished cross sectional area of the right and/or left pulmonary artery Three of the patients were siblings and in three the mother had rubella during the first trimester

ZUSAMMENFASSUNG

Die Verfasser prasentieren 11 Patienten mit supravalvularen Pulmonalisstenosen welche *alle mit der selektiven Angiokardiographie diagnostiziert worden* sind Funf hatten keine nachweisbare Herzanomalie Es wurden 4 verschiedene Typen der Stenose unterschieden singulare oder multiple Stenosen der lobaren Aste der Arteria pulmonalis eine Stenose bei der Bifurkation der Lungenschlagader eine membranöse Stenose unmittelbar distal der Pulmonalisklappe eine Stenose oder generelle Querschnittsverengerung der rechten und/ oder der linken Arteria pulmonalis Drei Patienten waren Geschwister und bei drei *anderen* hatte die Mutter Rubeola während des ersten Drittels der Gravidität

RÉSUMÉ

Les auteurs présentent onze cas de sténoses pulmonaires supravalvulaires tous diagnostiqués par angiocardiographie sélective *Cinq d entre eux ne présentaient pas d anomalie* cardiaque décelable Les auteurs distinguent quatre types différents de sténoses sténoses unique ou

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No treatment is available for the multiple peripheral stenoses but surgical correction has been performed in cases with central stenoses (20). The prognosis is unknown, but probably depends upon the severity of the stenoses and the presence of associated lesions. Additional defects compound the severity of the clinical condition, as was demonstrated in the two patients who died, one had aortic stenosis and the other a ventricular septal defect and a patent ductus arteriosus. Correction of associated lesions may definitely improve the prognosis, as was demonstrated by the patient in Case 5 who was in severe failure until a patent ductus arteriosus was ligated.

SUMMARY

Eleven patients with supravalvular pulmonary stenoses are presented, all diagnosed by selective angiocardiography. Five had no demonstrable heart anomaly. Four different types of stenoses were distinguished: single or multiple stenoses of the lobar branches of the pulmonary artery, stenosis at the bifurcation of the pulmonary trunk, membranous stenosis immediately distal to the pulmonary valve, stenosis or generally diminished cross sectional area of the right and/or left pulmonary artery. Three of the patients were siblings and in three the mother had rubella during the first trimester.

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multiples des branches lobaires de l artère pulmonaire sténose a la bifurcation du tronc pulmonaire sténose membraneuse immédiatement en aval de la valvule pulmonaire sténose ou diminution de calibre généralisée d une ou des deux arteres pulmonaires droite et gauche Trois de ces malades etaient frères ou sœurs et la mère de trois autres avait eu une rubéole au cours du premier trimestre de sa grossesse

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control The luminous flux is measured during the entire exposure with a special apparatus (Philips) The film is developed in ordinary roentgen developer and viewed in Arnos Roentgen Cine projector R G 35 the negatives need not be turned into positives, and the film may be put through the projector as often as desired The skin dose (about 20 mA at 90 to 120 kV) for a film of 25 metres length is about half that received in a routine examination of the stomach Field size about 13 × 13 cm Half the film is taken in the erect position p a, and the other half a p with the patient prone

Fifteen patients had not been referred for operation within 6 months of the first roentgen examination There was no doubt that the obstruction was not of a mechanical nature in all the five oldest of these patients These were not examined by cineroentgenography and the original findings were documented by ordinary roentgenography These cases were primarily classified as uncertain as far as surgical indication was concerned and all 5 made a clinical recovery Out of the 10 patients in whom the diagnosis at the first examination was based on cineroentgenography one refused to be examined again her clinical condition was unchanged Two patients were unable to attend The remaining 7 were roentgenologically unchanged or worse and 3 were operated upon and the roentgenologic findings confirmed Cineroentgenography thus appears to constitute a dependable method of examination Control examinations have shown the changes to be constant In the majority of patients the symptoms have persisted and only a few have been relieved by conservative treatment

Operation has been performed in 21 cases The follow up period is not long, and one recurrence at the end of 5 years indicates that it is still too early to be certain of the duration of the results of operation Bands fibrous adhesions, and abnormal dilatations of the duodenum have been found at operation and in the great majority of cases the operator interpreted the changes as *being due to* congenital malrotation Only a few patients had adhesions of a *different nature* e g following cholecystitis and, in one case, previous operation

Roentgen examination alone can hardly decide the *nature of the* obstruction If the obstruction is high in the duodenum it may be due to an annular pancreas we have seen two cases of this category which were published elsewhere (4) Obstruction caused by fixation due to malrotation is usually low seated but has occasionally been encountered at a high level Two patients had nervous anorexia One of them has been well for 6 years after operation and the other for more than 6 months The possibility of duodenal obstruction should be borne in mind in this condition SCHERMULY published cases in which the obstruction was due to nodal enlargement of an unknown nature but we have not encountered this condition

The difficulties in distinguishing true obstruction from dilatation due to duodenal ulcer have been mentioned Manifestations at the distal part of the duodenum are usually far less marked in ulceration than those seen in true obstruction



Fig 1 Duodenal ulceration with dilatation of lower part of duodenum



Fig 2 Arterio mesenterial obstruction (*confirmed* by operation)

wave but an image intensifier and cineroentgenography have shown this not to be the case Normally not more than one contraction occurs in 10 seconds, but in obstruction four contractions may be observed in the same period (Antiperistalsis in the form of cogwheel movements running forwards and back wards *along the edges of the duodenum is frequently observed in normal* subjects)

According to FISCHER the maximum width of the duodenal bulb at the base is 3 5 cm, with an average of *3* cm, its height is generally *3* cm and never exceeds 4 cm The duodenum like the jejunum normally has a diameter of 2 cm Retention of the barium emulsion in the stomach for more than 4 hours is commonly observed in cases of duodenal obstruction This applies particularly in ambulatory patients If the patient has been in bed and on a light diet for some days prior to the examination there is a risk that the condition may have improved by rest and the severity of the condition may be masked We have in the past 3 years used cineroentgenography for the examination of these *patients*

The film Kodak Fluoradak 35 mm (green sensitive) in 25 m lengths is inserted into a specially built Arriflex camera fitted to a 5 Philips intensifier and exposed under fluoroscopic



Fig. 4 Functional disorder in a case which appeared normal half a year later Sequence of films obtained during an exposure time of 2.5 seconds.



Fig 3 Fixation anomaly (confirmed by operation) Sequence of films obtained during an exposure time of 3 seconds

of fixation anomalies Gorn and Wilk assume it to be 5 in 1 500 roentgen examinations of the stomach and duodenum, which is probably about right Functional dilatation and dilatation due to duodenal ulceration are much more common

SUMMARY

The author reports a controlled series of 21 cases of duodenal obstruction Duodenal ulceration may sometimes be associated with duodenal changes similar to those seen in mechanical obstruction but usually less marked The differences between mechanical obstruction and functional dilatation are described The value of cineroentgenography is stressed

ZUSAMMENFASSUNG

Der Verfasser berichtet uber eine Untersuchung von 21 Fallen mit Obstruktion des Zwolffingerdarmes Duodenalulzeration kann manchmal mit Duodenalveranderungen verbunden sein *die denen ahneln welche bei mechanischer Obstruktion vorliegen jedoch gewohnlich* weniger markiert Die Unterschiede zwischen mechanische Obstruktion and funktionelle" Dilatation werden beschrieben Der Wert der Kinorontgenographie wird betont

RÉSUMÉ

L auteur présente une serie de 21 cas controles d occlusion du duodénum L ulcération duodenale peut parfois etre accompagnée de modifications duodénales semblables a celles que l on observe dans l occlusion mécanique mais habituellement moins marquées L auteur décrit les différences entre l occlusion mécanique et la dilatation fonctionnelle Il souligne l interet de la cineradiographie

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An 'enlarged duodenum' may be found in abnormalities other than duodenal ulceration Such conditions have been reported by many authors REBOULE, DELORME, BOYSSOU & COULON grouped the causes of a dilated duodenum as follows

1 Reflex phenomena due to conditions in the vicinity of the duodenal bulb (a) gastrobulboduodenal lesions including duodenal ulcer, (b) operations on the stomach, and c) inflammatory lesions of the gallbladder, pancreas, or appendix

2 Remote causes, such as brain tumours, nervous anorexia, and toxic conditions

FISCHER (1960) expressed similar views and also accepted the conception of true mechanical obstruction According to the French authors mechanical obstruction is distinguished by a far more 'brutal' appearance than non mechanical changes which they call 'functional' phenomena, an opinion I share The difficulty in distinguishing roentgenologically between 'functional' conditions and mechanical obstructions is most marked in the dilatation due to duodenal ulcer Our series abounds in functional findings which, as stated by the French authors, lacked the 'brutality' in appearance which would be expected if the stenosis were real, but in duodenal ulceration the appearances may at times be such that it is difficult to eliminate the possibility of mechanical obstruction

It may be that functional states and dilatation due to duodenal ulceration were not recognised as separate entities in the nineteen twenties and then were therefore both treated by operation

After the demonstration of a presumably mechanical obstruction, we usually try conservative treatment If, at the end of 3 months, the roentgen appearances are unchanged and the symptoms persist and are severe, we advise operation

Anomalies of the small intestine due to malrotation other than duodenal dilatation are of course often encountered but my reasons for collecting the latter into a special group are that they are particularly accessible to roentgenologic examination It must be stressed that an examination of the 'stomach and duodenum' is not complete until the whole of the duodenum as well as the proximal part of the jejunum, where functional' phenomena are apt to occur, have been carefully examined

Of the 21 cases subjected to operation, 15 recovered, 2 improved 2 remained unchanged, and 2 have been lost to follow up In 11 cases the operation consisted merely in freeing the adhesions while more radical measures were adopted in the remaining 10 cases

The condition appears to be more common in females than in males, in this material 14 were females and 7 males To these may be added our 2 cases in women, of annular pancreas which do not belong to those of fixation due to malrotation but have to be included among the obstructions These cases have already been published by RABBE It is difficult to state definitely the incidence

radiologic and clinical problems — on the other hand are more likely to confuse than to clarify the matter The technique recommended is at times *unorthodox The author uses* 24 × 30 films for the cervical spine and 35 × 42 cm films for the thoracic spine furthermore over exposed films are recommended Stereoscopic views are preferred to oblique views for the study of the intervertebral foramina That oblique views in the myelographic examination of lumbar disks are valuable is not even mentioned this may explain the author s somewhat surprising statement that herniations between L5 and S1 seldom cause indentations in the subarachnoidal space

The main part of the book is written by Decker himself He carefully describes the technique of the various contrast methods and discusses the indications and the hazards One chapter is devoted to vascular diseases of the brain and in another he gives a detailed description of the changes caused by brain tumours and related lesions All the chapters written by Decker are of great interest *Appreciation of the text is greatly facilitated by numerous illustrations* most of which are reproductions of roentgen films apparently from the author s very extensive material generally speaking they are of a good quality as well as being most instructive Some objections to the author s conclusions and statements may be raised he seems to be of the opinion that in cerebral angiography a very low common carotid puncture must be performed in those cases in which the artery bifurcates early in order to obtain a good filling of the intracerebral vessels It would appear to the reviewer that separate injections into the internal carotid artery and if necessary the external carotid artery are much to be preferred in all cases Ventriculography with Myodil is recommended in cases in which the third and fourth ventricle are not clearly demonstrated by gas The reviewer feels that even small changes should be demonstrable with gas if the technique is correct and executed carefully A typical film of a tentorial meningeoma supplied by a meningeal vessel arising from the internal carotid artery is illustrated in Fig 287c Unfortunately this case is described as one of a meningeoma of the lateral ventricle according to a personal communication this error is being corrected in part of the edition

In the chapter *Neuropsychiatrische Erkrankungen various types of brain atrophy and* congenital malformation are described as well as syringomyelia parasitic infestations neurofibromatosis sarcoidosis and several other lesions A review of intracranial calcifications is also included in this chapter

Ophthalmologists and otologists sometimes need the help of the neuroradiologist A special chapter by Decker and Metzger deals with the problems which may arise Decker together with Wiedenmann has also written two chapters on lesions of the spine and spinal canal They seem to employ mainly positive contrast media for the myelographic examination but in some of the illustrations gas is used as the contrast medium Many of the latter are not as clear as one would like but admittedly it is more difficult to obtain good reproductions of gas myelograms than of positive contrast studies

To summarize it may be said that the quality of this book is somewhat uneven — as is often the case when a publication is made up of contributions from several authors Some chapters are of great interest and can be warmly recommended both as an introduction to the subject and for those who want to extend their knowledge in neuroradiology Unfortunately parts of the book are only of limited value and should be accepted with some reserve

I Wickbom

BOOK REVIEWS

KLINISCHE NEURORADIOLOGIE Herausgegeben von K Decker 507 Seiten und 550 Abbildungen Georg Thieme Stuttgart 1960 *Price* DM 230

Some ten to fifteen years ago there was urgent need for good textbooks on modern neuroradiology This void has been largely filled in the past decade by works covering particular methods of examination and by others covering the whole field (e g in 'Lehrbuch der Rontgenologie by Schinz and in Handbuch der Neurochirurgie by Tonnis and Olivecrona)

The book now reviewed has a slightly different approach as indicated by the word klinische in the title This is reflected by a tendency to correlate the roentgenologic findings to the clinical signs rather than to the underlying lesion Fischgold and Metzger in their chapter on the indications for a special examination of the skull deal mainly with certain clinical syndromes They discuss for example sign complexes caused by lesions in the pontine angle the apex of the pyramid or the orbital fissure The differential diagnosis and the pathology of the lesions are only briefly mentioned

A few words should be said about the illustrations In textbook especially it is important of course that all the typical changes are represented and that the illustrations are clear and convincing This cannot be said of many of those in the chapter mentioned Even with appreciable experience in neuroradiology the reviewer must confess that he is unable to be convinced by several of the appearances described In some cases doubt even arises as to whether the author s interpretations are correct This is especially true of some of the single tomograms many are taken in an oblique projection and are of rather an inferior quality Without having the whole series of films available it is difficult to repudiate the conclusions drawn but some of the legends at any rate cause misgivings It is often not clear whether the diagnosis was confirmed at operation or autopsy In fig 7, for example an a p (or p a) tomogram of a patient with olfactory meningioma from the anterior part of the falx is compared to a normal a p (or p a) view The floor of the anterior fossa is said to be depressed although in this region and with this projection this is often a normal appearance The patient is said to have had no anosmia which is hard to understand if the floor of the anterior fossa were depressed Several other examples of statements that might cause misunderstanding could be mentioned

The clinical approach to the problem may sometimes prove advantageous as in the well written chapter by Decker on traumatic diseases

McRae in his chapter on epileptic fits gives some interesting viewpoints based on the large material from the neurologic institute in Montreal The main part of this chapter deals with asymmetry of the skull following injury of the brain tissue especially if this has occurred at birth or during early childhood Some of the illustrations used and the conclusions drawn are again not altogether convincing With reference to Fig 200 for example a passage reads With the technique used for the examination of the temporal horns no change of their size form or position can be seen in spite of a large cyst in the left temporal lobe As the temporal horns are incompletely filled in the lateral view with a vertical beam direction and as there are no a p views the examination was incomplete and therefore of limited value only

Taveras contribution dealing with neuroradiologic examinations in children and the chapter on radiologic problems in stereotaxic operations by Schunk and Mark are both clearly written and supply a long felt want Parts of the chapter dealing with disk degeneration —

LES CHONDRODYSTROPHIES GÉNOTYPIQUES. Par Maurice Lamy et Pierre Maroteaux. 120 pages, 100 illustrations. L'Expansion Scientifique Française, Paris 1960. Price NF 10.

Hereditary bone diseases present many problems in roentgen diagnosis. A classification of the different clinical forms is extremely difficult, and although several investigators including Wiedeman, Grebe and the authors of the book under review have endeavoured for the past two decades to solve the problem, complete success has not yet been reached. To use the genetic aspect as a starting point is not possible because of the existence of highly similar disease forms which in one case may be inherited recessively and in another predominantly. At the same time, a classification based on roentgen findings or on pathologic or histologic observations may be misleading owing to the fact that the general mode of reaction of the skeleton may be the same in diseases with entirely different origins. Furthermore, occupation and environment may cause considerable modifications of the syndrome in a disease of one and the same basic genetic origin.

The book under review gives an excellent account of the mode of inheritance and the clinical, roentgenologic and pathologic features in nine different conditions of the chondrodystrophy type. Multiple cartilaginous exostosis and dyschondroplasia (Ollier's disease) have also been counted as belonging to this disease type. If these conditions are included among the chondrodystrophies, it would seem equally logical to place other states, not treated in the book, in the same category. However, this is a matter of the scope of a work and constitutes a problem as difficult as that of classification.

The subject is presented in the clear, concise language of current French scientific literature. The authors' descriptions are of great value for those who wish to gain further information in this difficult field. The list of synonyms on page 13 is a welcome feature in a book on a subject with a terminology confused by unnecessary names of persons and ambiguous or misleading disease concepts.

Those investigators who encounter in their practice disease types discussed in the book will probably find that their cases constitute intermediate forms or other variants of the authors' types. This does not detract from the value of the work, which is warmly recommended to orthopaedists and radiologists interested in the skeleton.

S. Ribbing

ILEUS-KLINIK, RADIOLOGIE UND THERAPIE. Herausgegeben von R. Nissen und E. Hafter. 114 Seiten und 43 Abbildungen. Bibliotheca Gastroenterologica fasc. 3. S. Karger, Basel/New York 1961. Price sFr. 22.—

An interesting booklet of the proceedings of a symposium on intestinal obstruction which took place in Zurich in 1960 but containing nothing of particular roentgenologic interest.

J. Frimann-Dahl

L CARDIOANGIOGRAPHIC STUDIES OF THE MITRAL AND AORTIC VALVES By S R Kjellberg B Nordenstrom U Rudhe V O Bjork and G Malmstrom 85 pages and 45 figures Acta radiol (1961) Suppl No 204 Price Sw Kr 30

A fairly accurate diagnosis of the nature of the defect in certain valvular heart diseases may be obtained from the history, clinical examination, and ordinary roentgen examination of the heart and lungs Classic stenosis of the mitral valve is a case in point In many cases, however, the valvular lesion is combined with mitral insufficiency and changes in the aortic valves and even if the examinations are supplemented with pressure measurements in the aorta and the left ventricle and atrium it is often difficult to reach any definite decision as to the relative significance of the stenosis and insufficiency components in the mitral and aortic valves Valuable information regarding the various components may however be gained through the injection of contrast medium into the ascending aorta and the left ventricle and atrium Injection of a contrast medium into a site close to the valvular apparatus to be investigated is furthermore usually the only method by which details regarding the anatomy of the mitral and aortic valves may be obtained From the surgeon s viewpoint it is of the greatest importance to have as clear a picture as possible of the condition of the valves when an operation is to be undertaken to improve their function When contrast medium is to be injected into the left atrium a catheter can sometimes be inserted through a patent foramen ovale, if this aperture is not available the atrium must be punctured For selective contrast injection into the left ventricle a catheter can be inserted in a retrograde direction from a peripheral artery to the ventricle another method is to inject the medium through a needle which has been introduced into the left ventricle transthoracically Retrograde catheterization may be used for injection of the contrast medium into the left ventricle in most of the cases with normal conditions in the aortic valve when aortic stenosis is present however, it is not always possible to carry out this procedure In the investigation under review the authors performed cardioangiographies in 41 cases with injection of the contrast medium into the left atrium and in 34 cases with injection into the left ventricle after transthoracic puncture of the atrium and ventricle The possibility of studying the insufficiency component in the aortic valve by introducing contrast medium through a catheter into the ascending aorta is also illustrated in a few cases

Following a description of important features in the normal morphology of the left atrium and ventricle the anatomic appearance and normal action of the aortic and mitral valves are illustrated The chief aim of the investigation however was to study the changes in the atrium and ventricle as well as those seen in the aortic and mitral valves when pathologic conditions are present in the cusps The dome formation of the valves in stenosis the size of the constricted orifices and the thickness and mobility of the valves were studied and an attempt was made to assess the degree of insufficiency in the cusps There were two cases of pure mitral valve insufficiency in the material and the roentgen appearances in these were typical The material also contained cases of subvalvular aortic stenosis combined pulmonary and aortic stenosis and a combined mitral and aortic defect The contrast medium should be injected into the ascending aorta above the aortic valves for the investigation of the insufficiency component in the aorta The technique both for puncture with injection of the medium into the left atrium and into the left ventricle and for retrograde catheterization of the aorta is described The indications for the various examinations as well as the hazards and complications connected with them are also discussed

Iulorcncu

RADIATION PROTECTION AND RECOVERY Ed. by Alexander Hollaender 392 pages 55 illustrations and 22 tables Pergamon Press Oxford 1960 Price 70 sh

The question of spontaneous recovery from radiation damage and the possibilities of artificially alleviating or completely preventing such damage have in recent years attracted much theoretical and practical interest The present book edited by a leading authority in this field and written by a number of specialists on the different aspects of the matter is therefore welcome

After an introduction by the editor P Alexander writes on the protection of macromolecules in vitro D G Doherty on chemical protection of mammals and G E Stapleton on protection and recovery in bacteria and fungi while Anna R Whiting discusses the corresponding effects in cells in general S Wolff deals with chromosome aberrations D Davidson with the mechanisms of protection and recovery in seeds and roots and A D Conger writes on genetic protection A chapter by L H Smith and C C Congdon on treatment of acute whole body radiation injury in mammals is mainly devoted to transplantation of hematopoietic tissue and its clinical applications T T Odell Jr G E Cosgrove and A C Upton write on the modification of late somatic effects and T Makinodan and N Gengozian discuss the radiation effect on antibody formation The last chapter by J Jagger on photoreactivation is the only one which specially deals with the effects of short wave ultraviolet light many of which can be reduced or nullified by subsequent irradiation with light of a longer wavelength

The book gives a detailed account of the state of science in the various parts of the subject and contains a total of 1 548 references It provides no easy reading to those without some previous knowledge in the field but to those active in it the book should prove most useful

Sten Benner

LA RADICULOGRAPHIE LOMBAIRE DANS LA SCIATIQUE Par J Ecoiffier 140 pages 88 illustrations Masson Paris 1960 Price NF 40

Lumbar myelography with water soluble contrast media in spite of its undoubted advantages has not been generally accepted outside Scandinavia owing to certain complications connected with the examination Ecoiffier who studied radiology for a long period in Sweden introduced the method in France and in the book under review describes his experiences in over 700 examinations After a presentation of the anatomy physiology and pathology of the lumbar portion of the vertebral column the author describes his technique for lumbar myelography Considerable space is devoted to a description of the complications as well as to detailed methods for avoiding them The effects of various preparations for use in spinal anaesthesia and their importance for avoiding complications are however not discussed The results of the examinations are presented and the normal variations and roentgenologic appearances especially in protrusion of an intervertebral disk, are dealt with

The author unfortunately does not discuss the postoperative deformations of the dural sac which are however of great differential diagnostic significance in recurrent herniations

The work is well written and arranged and an analysis of the minor changes in the appearances of the nerve root sheaths indicates that it has been presented with care and thoroughness The high class roentgenographic illustrations and explanatory diagrams increase the value of the book which although it does not appear to break any new ground can be warmly recommended to all those interested in the problem of sciatica

Stig Fagerberg

LYMPHANGIOGRAPHIE UND LYMPHADENOGRAPHIE DER EXTREMITÄTEN Von Fritz Kaindl Eva Mannheimer Lilly Pfleger Schwartz und Bruno Thurnher 71 Seiten und 112 Abbildungen Georg Thieme, Stuttgart 1960 Price DM 39

In 1952 KINMONTH introduced his technique for injection of contrast medium directly into the lymph vessels since when the procedure has been widely used in the investigation of the anatomy pathology and physiology of the lymphatics The present authors were among the first to apply the method successfully, and this monograph is a survey of their experience It appears that the development in this field is still in its teething stage and the present publication may be somewhat premature However since this field is new and fascinating the book is valuable not only to those especially interested in the subject but also to those who wish to form a general opinion of our present knowledge in the field

The concise surveys beautiful illustrations and excellent design of the book make its contents easy to digest The opening chapter gives a historical review and a brief description of the gross anatomy of the lymph system This is followed by a detailed presentation of the histology of the lymphatics and is valuable because of the few comprehensive surveys available of the histology of the lymphatics in man Microscopic changes in conditions of disease are described and are evidently based on a large material It is interesting to note that the authors make a distinction between lymphangitis obliterans and other hypoplastic primary lymph angiopathies Apart from this they adopt Kinmonth s classification of diseases of the lymphatics The frequencies of the various types are not given Secondary lymphatic diseases are discussed and the changes often severe in chronic venous lesions of the legs are described

Diseases of the lymph vessels occupy the major part of the book and it is only too evident that our methods of diagnosis are still far from perfect The difficulties are mainly due to imperfections of the contrast media a more detailed discussion of which would have been an advantage

The authors give a very detailed list of references which increases the value of the monograph

Sten Johansson

THE SPECTRA OF X RAYS SCATTERED IN LOW ATOMIC NUMBER MATERIALS By W R Bruce and H E Johns 57 pages 18 illustrations and 8 tables British Journal of Radiology Supplement No 9 London 1960 Price 12sh 6d

This book describes analytic and Monte Carlo methods in which a punched card computer was employed for calculating the spectral composition of scattered roentgen radiation in a low atomic number scatterer The results are presented in a number of graphs and tables which show central axis data for primary radiations of 50 to 1 250 keV for a pure Compton scatterer water and aluminium all for an infinite field area In the case of water the results are also given for field sizes from 25 to 400 cm² Apart from spectral data information is given which permits the calculation of depth doses and back scatter factors The results are compared with experimental data and theoretical results obtained by other methods and good agreement is found Although this book is unlikely to have a wide appeal there are many workers who will find it of great value

Sten Benner

RADIATION PROTECTION AND RECOVERY Ed by Alexander Hollaender 392 pages 55 illustrations and 22 tables Pergamon Press Oxford 1960 Price 70 sh

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Stig Fagerberg

Die intraoperative Röntgenbestrahlung des Mammakarzinoms Von E Muntean 108 Seiten, 9 Abbildungen und 26 Tabellen George Thieme, Stuttgart 1961 Price DM 17 50

This book reviews the development of the operative and radiologic methods used in the treatment of mammary cancer and the value of the different techniques gathered from an obviously extensive knowledge of the literature is reviewed and discussed The advantages and disadvantages of pre operative radiation therapy with varying dose levels are considered from the aspects of the biologic effect on the tumour cell the surrounding tissues the incidence of recurrence and the prognosis for the patient Other factors of significance to the outlook such as biopsy and the time interval between radiation and operation or between operation and radiation have also been studied A special chapter is devoted to the possibility of dissemination of the cancer cells through the blood and lymph systems of the mammary gland

The author s own material comprised 125 operable cases 39 of these had received radiation only postoperatively 11 only pre operatively and 75 both pre and postoperatively Roentgen therapy was applied according to the conventional scheme (180 kV a filter of 2 mm Cu + + 1 mm Al FSD 30 cm daily dose 200 r/skin total dose 1 000 to 2 000 r/skin) The radiation was administered to the breast at a tangent through two or three portals and to the axilla and fossa supraclavicularis through one anterior and one posterior portal The operation was performed 9 to 14 days later

Despite the comprehensive in some instances tedious recording of 880 works the book gives no new viewpoints on the problems relating to the treatment of mammary cancer A much larger material than that presented by this author examined by standardized clinical and histologic methods and with identical operative and radiologic treatment is required before the value of pre operative radiation therapy can be finally assessed

However for those who are interested in these problems the book should be worth reading as a stimulus to further discussion and as a comprehensive source of references

Gustaf Notter

BOOKS RECEIVED

We acknowledge with thanks under this heading books received *for review* which we trust will be regarded as a sufficient mark of appreciation of the courtesy of the sender The reviews of selected items will appear as soon as opportunity affords

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EFFECTS OF IONIZING RADIATION ON THE HUMAN HEMAPOIETIC SYSTEM Publication 874 National Academy of Sciences National Research Council Washington 1961

EFFECTS OF VARIATIONS IN THE AMBIENT AIR ON THE CALIBRATION AND USE OF IONIZATION DOSEMETERS National Physical Laboratory Her Majesty s Stationery Office London 1960

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ZIEDSES DES PLANTES, B G Subtraktion Georg Thieme Stuttgart 1961

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ROENTGEN DIAGNOSIS

Nervous system

Digestive tract

Heart and Vessels (incl lymphatic vessels)

Lungs, Pleura, Mediastinum and Chest walls

Bones and Joints

Ear, Nose and Throat

Uro-Genital system

RADIOTHERAPY

CHEMOTHERAPY

RADIOACTIVE ISOTOPES

RADIOPHYSICS

RADIOBIOLOGY

TECHNIQUE

Roentgen examinations

Contrast media

Protection and Injuries

BOOK REVIEWS

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(r) indicates 'reviewed only'

List of Supplements to Acta Radiologica

(Issued by December 1961)

For Suppl. Nos. I—XXII inclusive see list issued by December 1960 in Vol. 54 fasc. 6. The information given therein is still valid.

The supplements are published from time to time and are not included in the subscription rate. Prices and year of publication of numbers already issued are detailed below.

XXIII. H. Ahlbom: Mucous and salivary gland tumours. 1935. *Price Sw. Kr. 20:—*

XXIV. E. Lysholm: Das Ventrikulogramm. I Teil. 1937. *Price Sw. Kr. 10:—*

XXV. E. Lysholm: Das Ventrikulogramm. II Teil. 1937. *Price Sw. Kr. 15:—*

XXVI. F. Lysholm: Das Ventrikulogramm. III Teil. 1935. *Price Sw. Kr. 12:—*

XXVII. H. Hellmer: Röntgenologische Beobachtungen über die Ossifikation der Patella. 1935. *Price Sw. Kr. 10:—*

XXVIII. F. Knutsson: Urethrography. 1935. *Price Sw. Kr. 12:—*

XXIX. O. Kaalund-Jorgensen: Experimental studies on a transmissible myelomatosis *(reticulosis) in mice.* 1936. *Price Sw. Kr. 12:—*

XXX. K. Lindblom: A roentgenographic study of the vascular channels of the skull. 1936. *Price Sw. Kr. 10:—*

XXXI. S. Grettve: Morphologische und tierexperimentelle Studien über das Schleimhautrelief des Magen-Darmkanals. 1936. *Price Sw. Kr. 10:—*

XXXII. H. Wulff: Die Zuverlässigkeit der Röntgendiagnostik — besonders hinsichtlich des Wertes der Urographie — und die Prognose bei Nieren- und Harnleitersteinen. 1936. *Price Sw. Kr. 15:—*

XXXIII. J. Frimann-Dahl und G. Waaler: Röntgenologische und pathologisch-anatomische Studien über den tuberkulösen Primärkomplex. 1936. *Price Sw. Kr. 9:—*

XXXIV. S. Ribbing: Studien über hereditäre multiple Epiphysenstörungen. 1937. *Price Sw. Kr. 8:—*

XXXV. A. Renander: Le traitement radiologique de l'actinomycose. 1937. *Price Sw. Kr. 8:—*

XXXVI. G. Jonsson: Malignant tumors of the skeletal muscles, fasciæ, joint capsules, tendon sheaths and serous bursæ. 1938. *Price Sw. Kr. 20:—*

XXXVII. B. Lilja: Displacement of the calcified lineal body in roentgen pictures as an aid in diagnosing intracranial tumors. An anthropometrical statistical analysis. 1939. *Price Sw. Kr. 10:—*

XXXVIII. King Gustaf V:s Stockholm Jubilee Clinic. 1939. *Price Sw. Kr. 8:—*

XXXIX. G. Fr. Petersen: Röntgenologische Untersuchungen über Arteriosklerose. 1941. *Price Sw. Kr. 8:—*

XL. T. Denstad: Über die Bedeutung der Röntgenuntersuchung für die Kardiologie. 1941. *Price Sw. Kr. 8:—*

XLI. A. Renander: The roentgen density of the cystine calculus. 1941. *Price Sw. Kr. 15:—*

XLII. S. Welin: Beiträge zur Röntgendiagnostik der Otitis media acuta und ihrer Komplikationen im Schläfenbein. 1941. *Price Sw. Kr. 20:—*

XLIII. S. R. Kjellberg: Hystero-Salpingo-Pelvigraphie. 1942. *Price Sw. Kr. 15:—*

XLIV. Carl Krebs, Oskar Thordarson and Johannes Harbo: Experiments with mammalian sarcoma extracts in regard to cell free transmission and induced tumor immunity. 1942. **(Out of print.)**

XLV. J. Torgersen: The muscular build and movements of the stomach and duodenal bulb. 1942. *Price Sw. Kr. 15:—*

List of Authors

(r) indicates 'reviewed only'

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